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CLINICAL APPLICATION OF THE THIOCHROME REACTION IN THE STUDY OF THIAMIN (VITAMIN B_1) DEFICIENCY *

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A CHEMICAL method for the estimation of thiamin (vitamin B_1), should have the advantages, as compared to biological assay, of speed, accuracy, cheapness, and ease of performance. The great advantage of biological assay is definite specificity. However, under well controlled conditions the uncertainties of chemical assay may become negligible.

Of the several methods proposed for the chemical estimation of thiamin, the thiochrome method of Jansen [1] has received the most attention. Recently, the method of Prebluda and McCollum [2] as modified by Melnick and Field [3] has been shown to possess a high degree of specificity and accuracy, but the technic as described seems too complex for ordinary clinical purposes. Schultz et al.[4] have developed a fermentation test for vitamin B_1 which apparently is rapid and sufficiently specific for most purposes.

The phycomyces growth method of Schopfer,[5] applied to various materials by Meiklejohn,[6] Bonner,[7] and Rowlands,[8] may prove to be of considerable value as a comparatively simple method of biological assay suitable for clinical investigation.

The purpose of this paper is to relate experiences with the thiochrome method as applied to urine in study of the metabolism of thiamin in normal and thiamin deficient subjects, with special attention to the possibility of diagnosis of thiamin deficiency states.

Using the bradycardia method of bioassay, Harris and his associates [9] showed that the urinary excretion of thiamin depends upon the amount ingested; that subjects on adequate diets excrete in the urine more thiamin than patients with varying degrees of deficiency. In 24 hours normal sub-

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jects excreted from 12 to 23 International Units of thiamin on a "normal" diet, and from 36 to 76 International Units after oral administration of a vitamin B concentrate containing 340 I.U. (i.e., about 10 to 20 per cent of the test dose). Patients on inadequate diets, with and without definite deficiency disease, excreted much less; those with frank beri-beri, the least. Using a modification [10] of the original thiochrome method, Westenbrink and Goudsmit studied the urinary excretion of thiamin in normal subjects, in pregnant women with and without manifestations of thiamin deficiency, and in patients with arrested tuberculosis.[11] They demonstrated that the substance (presumably thiamin) estimated by the thiochrome method did fluctuate in amount in the urine just as thiamin would be expected to fluctuate under the various experimental conditions, thus demonstrating a degree of specificity in this method sufficient for clinical purposes at least. The urinary excretion of thiamin was found to be dependent on the amount ingested, and decreased rapidly to a low level in three days with the subjects on deficient diets. An estimate of the degree of depletion could be made by finding the number of oral test doses required for the 24-hour excretion to become normal. Normal subjects usually excreted more than 100 gamma (80 to 300) in 24 hours. Oral administration of pure thiamin in moderate doses (3 to 5 mg.) resulted in increased excretion beginning in the first hour, reaching a peak in the second or third hour, and complete in about five hours. Larger doses often resulted in increases of excretion extending into the second 24-hour period. The per cent excreted in 24 hours varied considerably with the size of the dose and the frequency of administration. About 15 per cent was excreted after a single 3 mg. dose, 8 to 10 per cent after a single 5 mg. dose, 5 per cent after a single 20 mg. dose, and 10 per cent after administration of 20 mg. in divided doses (i.e., the percentage excreted depended upon the size of the individual dose rather than upon the total dose given during the day).

Intramuscular injection gave a maximum excretion in the first hour, with the subsequent excretion about the same as after oral administration when doses of moderate size were used. The larger the amount injected, the greater was the per cent excreted (5 per cent of 1 mg., 10 per cent of 3 mg., 20 per cent of 10 mg.). By the use of parenteral test doses no significant differential in excretion was found between normal and thiamin deficient subjects, so that the parenteral method was considered of no value for diagnosis of deficiency.

Pregnancy was found to exert a marked influence on thiamin excretion, as pregnant women excreted considerably less thiamin than non-pregnant women presumably on similar diets. A group of pregnant women without symptoms referable to thiamin deficiency excreted significant, although subnormal amounts, both before and after the administration of test doses, while another group with symptoms, of the same economic class, excreted very much less, and often required several test doses before any thiamin was detected in the urine.

Karrer and Kubli,[12] using their modification of this method, found the excretions to be of about the same magnitude as those found by other investigators, the results with the thiochrome method varying by about 20 per cent from the results of assay with the bradycardia method. However, the latter method is hardly sufficiently constant and accurate to serve as the basis for estimating the error of the thiochrome method.

Pyke,[13] using crystalline thiamin and acid-clay adsorbates, found a high degree of correlation between the thiochrome method and bioassay. Ritsert [14] applied the thiochrome method to feces as well as urine, and found 100 to 400 micrograms of thiamin in the feces of normal men in 24 hours. Of a single 10 mg. dose 4 to 6.5 per cent was found in the urine, and 20 to 25 per cent in the feces. The high fecal excretion points to incomplete absorption of large doses.

Method

The method to be described depends upon the following reaction: Thiamin oxidized by the appropriate amount of ferricyanide in strongly alkaline solution is converted quantitatively (Jansen) into thiochrome, which fluoresces intensely blue in ultra-violet light. The intensity of the fluorescence varies with the amount of thiochrome present, and may be measured either with a photo-electric cell [1, 10, 13, 18] or by visual comparison with standards.[12, 14, 15]

Our present technic is as follows: The urine (usually a 24-hour specimen) is collected in 10 ml. of glacial acetic acid. A portion (usually 5 ml.) is diluted with 10 volumes of water to inhibit adsorption of interfering substances,[10] is acidified with glacial acetic acid until acid to congo red, and is then shaken for 10 to 15 minutes with 300 mg. of Lloyd's reagent.* After filtration by suction, the adsorbate is washed with water acid to congo red, and dried with 95 per cent alcohol followed by ether. Two 100 mg. portions are weighed into glass-stoppered flasks (cork and rubber stoppers would contribute fluorescent substances) and to one portion are added successively 2 ml. methanol, 1 ml. water, and 0.6 ml. 1 per cent potassium ferricyanide. After mixing thoroughly, 1 ml. of 30 per cent sodium hydroxide is added, and the mixture shaken gently for about a minute. The thiochrome formed is extracted by shaking vigorously for a minute with 10 ml. isobutanol (previously saturated with water to avoid variable changes in volume). On standing or centrifuging, the mixture separates into two layers, with the alcohol layer (10 ml.) on top. This may be clarified by filtration (the use of filter papers which furnish fluorescent substances should be avoided) or by drying with anhydrous sodium sulfate, although visual comparison is facilitated by the more even illumination found in the turbid solutions. The suspended water does not interfere with the estimation.

* Some adsorbent earths lose considerable weight in this procedure, and must be weighed *after* the adsorption and drying. Our Lloyd's reagent loses no weight.

The second portion of adsorbate is treated in exactly the same way, except that the ferricyanide is omitted. This " blank " contains the non-specific fluorescent substances carried over from the urine, but no thiochrome.

A standard solution of thiochrome is prepared by oxidation of 20 gamma of thiamin chloride without preliminary adsorption, using exactly the same amounts of reagents and the same aqueous volume. Since the aqueous volume is the same in the standard and the unknowns there is automatic compensation for the loss of thiochrome remaining in aqueous solution which is not the case when the standard is prepared with a very small aqueous volume, as in the procedures described by some other authors.* The standard may now be considered to have the equivalent of 2 gamma of thiamin per milliliter.

A 5 ml. portion of the " test " solution is placed beside a similar portion of the " blank " solution in a simple comparator in which ultra-violet light from a small mercury arc † falls upon the tubes perpendicular to their long axes. Optically matched tubes are used for the two portions. The fluorescence is viewed from above. This procedure has seemed somewhat easier than comparison of the intensities by viewing from the sides or at an angle since the fluorescence appears to be concentrated in a small area. Confusing reflection is therefore avoided. Visible light from the arc is screened out by a filter (Corning No. 586). The reading is made in a darkened room.

If the specimen contains a significant amount of thiamin the " test " solution will have a blue fluorescence as well as the variable amounts of green from normal constituents of the urine, while the " blank " will exhibit only the " non-specific " green. Enough of the standard thiochrome solution (diluted 1:5 with isobutanol for most specimens) is added from a burette to the blank to make the intensities match. Volume changes are compensated for by addition of isobutanol to the " test." The amount of thiamin may then be calculated readily. Duplicate readings within 5 per cent are made easily in assaying pure thiamin, in amounts varying from 0.05 to 3.0 gamma in the 5 ml. isobutanol solution. It is less easy to compare solutions prepared from urine, because of the polychromatic fluorescence (blue through green). This difficulty is eliminated by viewing the fluorescence through a blue color filter.‡

Use of Methanol

As the work of Jansen and Westenbrink [1, 10] has shown, methanol in some manner protects the reaction against excessive concentrations of ferricyanide. If methanol is used as described, 0.6 ml. of 1 per cent ferri-

* With this procedure the ratio of the concentration of thiochrome in aqueous layer to that in alcohol layer is about 1:2.4.

† The inexpensive " H_4 lamp " manufactured by General Electric and Westinghouse gives very satisfactory results without excessive heat production.

‡ Wratten gelatin filter No. 47 (Eastman) has transmission characteristics suitable for this purpose.

cyanide solution will serve for quantities of pure thiamin varying from 1.0 to 20 gamma (the range tested), with variations of about 10 per cent, which is little more than the error of the actual comparison. When methanol is not used, the amounts recovered are much more variable whether or not preliminary adsorption has been carried out. In preparation of the standards, if methanol is used, the quantities of thiochrome obtained with amounts of ferricyanide ranging from 0.02 to 1.0 ml. of the 1 per cent solution vary not more than 10 per cent. Table 1 shows results in the assay of urine.

TABLE I

Urine Specimen (Micrograms per 24 Hours)

	1	2	3	4	5	6
With Methanol	365	345	800	500	180	25
Without Methanol	65	170	630	270	95	15

ADSORPTION

In an attempt to simplify the procedure, urine was treated without preliminary adsorption (1–5 ml.). Usually the results were a little higher (table 2), indicating minor losses in the adsorption.

TABLE II

Urine Specimen (Micrograms per 24 Hours)

	1	2	3	4	5	6	7	8	9	10
Adsorbate	210	195	110	102	115	75	30	245	245	85
Urine	250	220	160	92	130	80	30	290	255	95

Under certain conditions readings were inaccurate or impossible unless the adsorption technic was used. The urines of patients taking aspirin, codeine, or quinine, when treated directly produced "blanks" with intense blue fluorescence, often much stronger than that of the oxidized portion. A similar result was obtained in testing urines of a patient with severe pernicious anemia who had not been taking any drugs, and had had no liver extract. This is reminiscent of the difficulties encountered in applying the thiochrome method to assay of liver.[16] That this was not caused by oxidation of thiamin to thiochrome in the blank is indicated by: (1) the intensity of the "blank" fluorescence which may be many times the possible maximum due to thiamin; (2) its independence of the intake of extra thiamin; and (3) its dependence on the intake of the drugs noted, except in the last case in which it may be related to abnormal pigments.

Because of the possible errors in oxidizing specimens without preliminary adsorption, the adsorption technic was adopted as the routine procedure.

Interfering Substances

The drugs mentioned above interfere only if the adsorption technic is not used. Red pigments have been found in the urines of pellagrins, often in association with substances, presumably coprophyrins, which are fluorescent in ultra-violet light and soluble in acid-ether. This pigment, which Watson [17] suggested might be indirubin, is adsorbed by the Lloyd's reagent, which it colors red, and interferes with the reading chiefly by imparting to the " blank " the property of inhibiting the fluorescence of added thiochrome. It apparently is changed in the oxidized portion to a substance which does not inhibit the thiochrome fluorescence.

Bile interferes with the estimation, apparently more by inhibition of the fluorescence of thiochrome than by inhibition of the formation of thiochrome. If the highly colored " blanks " are used in the usual fashion, a large quantity of thiochrome may be added without imparting to the " blank " the characteristic blue fluorescence. If, however, pure isobutanol is used in place of the " blank " solution a comparison may be made, although the results are less accurate. By this procedure thiamin added to urine containing bile is recovered to the extent of about 80 per cent.

These interfering pigments may be removed fairly effectively by preliminary extraction of the urine with an equal volume of isobutanol. About 5 per cent of the thiamin is lost by this procedure. The green-fluorescent substances present in normal urine are not removed by isobutanol or by ether well enough to make extraction worth while, despite the advocacy of the former by other workers.[14, 31] *

Recovery of Thiamin Added to Urine

Table 3 indicates not only that added thiamin may be recovered adequately, but also that the same quantity of reagents may be used for widely differing amounts of thiamin in urine.

Normal Excretion

Table 4 summarizes data obtained by testing a group of interns and laboratory workers whose diets were known to be rich in thiamin. Test doses of 0.1 mg. of thiamin per kg. of body weight were given. This amount was adopted somewhat arbitrarily, but it has given good results in distinguishing various degrees of deficiency. In all subsequent tables the

* Recently we have used synthetic zeolite (Decalso) as the adsorbent, as suggested by Hennessy and Cerecedo.[18] This has the great advantage of adsorbing practically none of the non-specific fluorescent substances present in normal urine, so that the reading is made much more easily; 500 mg. of finely ground acid-washed (Decalso) are shaken with the urine (diluted 1 : 40 with water) and treated just as described for the Lloyd's reagent. Recoveries of thiamin added to urine range from 90 to 95 per cent. The red pigment to which reference has been made in the urines of pellagrins is very little adsorbed. The amount of ferricyanide required for the oxidation is much less, but recoveries are practically the same (variation 5 to 10 per cent) over a range of 0.1 to 0.6 ml. 1 per cent ferricyanide. Interference from bile pigments is practically eliminated.

size of the test dose recorded was determined on the same basis unless otherwise stated. The doses were given before breakfast.

In table 4 and all subsequent tables the excretion is expressed as a per-

TABLE III

Recovery of Thiamin Added to Urine

Subject	Gamma Present	Gamma Added	Gamma Found	Per cent Recovered
D. H.	0.58/15 ml.	1.0	1.51	93
	0.58/15	2.0	2.49	95
H. B.	0.13/7.5	1.0	0.94	81
	0.13/7.5	2.0	1.69	84
	0.13/7.5	3.0	2.46	82
	0.20/10	2.5	2.20	80
	0.20/10	5.0	5.00	96
	0.20/10	7.5	7.20	96
M. C.	1.3/10	1.0	2.2	90
	1.3/10	2.0	3.0	85
	1.3/10	3.0	4.0	89
	1.3/10	4.0	5.0	90
M. S.	0.74/10	5.0	5.4	94
	0.74/10	10.0	10.6	98
	0.74/10	15.0	15.3	97
	1.33/5	2.0	3.24	95
	8.2/10	2.0	10.2	100

TABLE IV

Normal Subjects

Subject	Gamma 24 Hours Resting	Test Dose mg.	Per cent Excreted 24 Hours	Gamma/ 100 ml. Urine	Comment
S. A.	200; 290	7	18.1	50	Diet unusually rich in B_1
E. B.	—	7	15.5	91	
C. F.	—	6.6	8.6–11.6	54–71	Serial estimations, daily for 2 weeks
M. F.	110	7	11.1	78	
D. H.	75; 90	5	11.0	55	
M. B.	—	7	10.4	94	12 hour excretion; developed catarrhal jaundice shortly afterward
E. P.	95	5	10.0	21	
H. F.	—	8	9.8	43	
A. G.	230	6	9.6	45	
J. C.	—	8	9.4	42	
M. B.	—	5	9.3	37	
D. T.	—	6	8.2	61	
F. C.	250	6	7.8; 9.5	28; 52	
P. C.	—	6	8.8	33	
H. B.	110; 220	7.5	6.7	42	12 hour excretion
L. G.	155	8	6.0	60	12 hour excretion
J. T.	—	6	6.9; 6.1	41	12 hour excretion
R. W.	—	7	3.9; 3.5	50	5 hour excretion (diet poor past week)

centage of the dose. The intake of thiamin in food is disregarded, since it cannot be estimated accurately, and since the test dose is large in comparison with the dietary thiamin.

Estimations of the excretions after doses of varying amounts have given results substantially in agreement with those found by other investigators; that is, the larger the dose administered orally, the smaller the per cent excreted. Westenbrink [10] thought this to be the result of increased destruction of thiamin in the tissues. Borsook,[19] using thiamin containing radioactive sulfur, showed that a large amount of the thiamin administered is destroyed in the tissues, the sulfur being excreted as ethereal sulfate. The work of Ritsert [14] showed that the feces contain as much as 25 per cent of a 10 mg. dose. Schultz et al.[4] showed that in animals fecal vitamin B_1 was considerably increased by moderate doses of thiamin by mouth. It appears, therefore, not only that a large dose is incompletely absorbed, but also that an excess is rapidly destroyed.

On the other hand, the percentage excreted after intravenous administration increases with increasing doses: about 15 per cent after 3 mg., 20 to 30 per cent after 7 to 10 mg., 50 per cent after 30 mg., and 80 per cent after 50 mg. By far the largest part of the excreted thiamin is found within the first hour.

It is apparent that thiamin is utilized more efficiently in small doses given frequently, either orally or parenterally, than in large single doses.

The data in table 5 are typical of 24-hour excretions after a long period of dosage with crystalline thiamin or crude concentrates given in divided doses.

TABLE V

Excretions after Long Continued Administration of Vitamin B_1

Patient	Dosage and Duration	Excretion Gamma per 24 Hours	Per cent of dose
L. B.	200 I.U.* twice daily 10 days	400	39
C. S.	200 I.U. twice daily 3 weeks	400	39
L. B.	200 I.U. thrice daily 2 weeks	500	25
E. R.	200 I.U. thrice daily 10 weeks	605–760	30–38
F. T.	200 I.U. thrice daily 5 weeks	690	35
L. G.	200 I.U. thrice daily 3 weeks	515–680	26–34
E. L.	200 I.U. thrice daily 4 weeks	550	28
E. S.	3 mg.† thrice daily 3 weeks	1300–1080	14–19
F. B.	3 mg. thrice daily 3 weeks	2100	23
A. H.	3 mg. thrice daily 2 weeks	1130	12
E. E.	1 mg. thrice daily 4 weeks	760	25

* B Complex. † Synthetic thiamin chloride.

It has been shown [10] that in normal subjects on a thiamin-poor diet for two or three days the 24-hour excretion was reduced to 40 micrograms. It appeared, therefore, that estimation of the excretion without administration of a test dose would in many instances indicate only the adequacy of the diet

during the past few days. Therefore, as a routine procedure in the outpatient department where collection of more than one 24-hour specimen would be difficult, usually only the excretion after administration of the test dose was estimated. Tables 5 to 16 summarize data obtained on several groups of patients. In most cases a detailed dietary history was obtained, but the well known inaccuracy and variability of data on the thiamin content of foods make it presumptuous to assign figures to the probable thiamin content of the diets. The term "good" indicates a diet obviously good, in which no important source of calories is thiamin-poor; "poor" indicates a diet so low in thiamin that one might reasonably expect to find more or less obvious manifestations of thiamin lack; and "fair" indicates the broad range between these extremes.

Thyrotoxicosis

Tests were carried out on thyrotoxic patients who had been in the hospital for about a week, on very good diets (see table 6). In the study of

Table VI

Patients with Thyrotoxicosis Tested During the Period of Pre-operative Care

Patient	Diet	Resting 24 hrs.	BMR	Dose mg.	Per cent Excreted	Gamma/ 100 ml. Urine	Comment
M. W.	Poor	—	—	5	2.1	16	Auricular fibrillation; congestive failure; pneumonia
P. J.	Fair	13	44%+	6	3.0	13	Apathetic; cardiac damage; post-operative hypothyroidism
V. B.	Fair	—	38%+	5	3.0	15	Auricular fibrillation
L. C.	Fair	—	58%+	5.2	3.6	7	Anorexia; post-operative hypothyroidism
A. B.	Fair	80	45%+	6	4.3	26	Recent improvement in appetite and weight
M. P.	Fair	—	85%+	4	4.7	19	Emaciated; disoriented; mild anemia
H. J.	Good	40	31%+	5	4.8	7	Anorexia; moderate anemia
G. K.	Good	100	42%+	7	4.9	8	Moderate alcoholic; rapid weight loss
M. P.	Fair	150	64%+	4	5.0	9	Emaciated; cardiac damage
C. H.	Fair	30	29%+	6	5.2	13	Marked asthenia; cardiac damage
H. C.	Good	120	46%+	7	6.3	37	Cardiac damage
T. C.	Good	—	66%+	6	6.5	13	Excellent appetite; marked weight loss
L. W.	Fair	8	47%+	—	—	—	Well controlled diabetes; asthenia; anorexia

these patients several factors of importance were noted. Most of them excreted very large quantities of urine, up to four and five liters daily. Many had been satisfying their increased appetites by increasing considerably their intakes of carbohydrate food, often in the form of vitamin-poor candy and

pastry. It is thought that the requirement for thiamin depends either upon the total caloric intake [20] or upon the intake of carbohydrate,[21] so that, despite a fairly good intake of protective foods, the production of mild deficiency in these patients was believed to be related in part to an uncompensated excess of carbohydrate. A comparison of this group with the normals reveals a moderate decrease in the percentage of thiamin excreted by the thyrotoxic group. That this is not a complete picture of the degree of deficiency is suggested by the differences between the groups noted in the columns "gamma/100 ml. urine." Cowgill et al.[22] showed that dogs subjected to diuresis developed signs of B_1 deficiency earlier than dogs on the same diet without diuresis. It might be reasonable, then, to suppose that the percentage of the standard test dose excreted by normally saturated persons excreting large volumes of urine would be somewhat higher than that of normals excreting normal amounts of urine; and that, in estimating the degree of thiamin saturation, the urinary volume as well as the per cent excreted must be taken into account.

Support for this hypothesis was provided by serial estimations carried out on some of the subjects. Two normal subjects excreting 1000 to 1500 ml. of urine daily took the standard test dose daily for a week. In both cases the excretion remained about the same from day to day, i.e., 8 to 11 per cent. The excretion of the thyrotoxic patient, T. C., whose urinary volume was consistently from 3000 to 5000 ml. did not "level off" until an excretion of 17 to 22 per cent was reached. Shortly before operation he voluntarily reduced his fluid intake to from 1500 to 2000 ml. and the excretion dropped to from 10 to 10.9 per cent. Similar results were noted in several other patients. An alternative explanation, not as yet supported by experiment, might be impairment of the liver function in thyrotoxicosis resulting in decrease in the phosphorylation of thiamin with consequent elimination in the urine. On the other hand, in patient A. B. whose urinary volume ranged about 1000 ml. the excretion "leveled off" at 12 per cent.

Within the normal range of urine volume (750 to 2000 ml.) little differences in excretion are noted.

Typical Thiamin Deficiency Neuritis (Table 7)

In three patients, hospitalized for treatment for severe alcoholic neuritis, in whom it was possible to make daily estimations, it was found that excretions approaching the normal occurred after 60 to 100 mg. of thiamin had been given in doses of 3.3 mg. two or three times a day together with a high vitamin diet. In from 17 to 25 days the excretions "leveled off" at from 17 to 26 per cent of the dose. (These high percentages, it must be remembered, are of small doses given frequently, and are not comparable to the lower percentages found with the standard test doses.) The total doses given before the "leveling off" occurred amounted to from 100 to 125 mg. One may not conclude that these figures represent the total deficit, since it

may be that in chronic alcoholism with possible liver damage there is a decrease in the ability to convert thiamin into cocarboxylase for storage and utilization. The hypothesis that liver damage increases the excretion of thiamin is supported by serial studies in three patients with hepatic cirrhosis in whom the excretions " leveled off " at from 17 to 26 per cent of the standard single test dose given daily. In none of these patients did the urine output ever exceed 1000 ml., so that diuresis played no part in these high excretions. Ochoa and Peters [29] and Westenbrink and Goudsmit [16] have shown that after parenteral administration conversion of thiamin into cocarboxylase takes place largely in the liver and kidneys.

TABLE VII

Patients With Frank Neuritis Caused by Nutritional Deficiency

Patient	Resting Gamma/24 hrs.	Test dose mg.	Per cent Excreted 24 hours	Gamma/100 ml. urine	Comment
N. J.	0	10	0.2	5	Alcoholic; pellagra
R. H.	—	3.3 Twice daily (under treatment)	0.3	2	Alcoholic; "wet beri-beri"; had had 33 mg. thiamin orally prior to first test.
L. D.	—	6	0.3	1.4	Alcoholic; psychosis
D. D.	0	—	—	—	Alcoholic
C. A.	0	5	0.9	7	Alcoholic; anemia; osteoporosis with pathological fracture
T. V.	—	6	1.0	15	Chronic neuritis; moderate alcohol; high vitamin diet two weeks
F. D.	25	11	1.5	7	Mild "post-influenzal neuritis" 4 weeks; well in 48 hours with thiamin orally
K. H.	25	6.7	3.6	26	Mild long-standing "alcoholic neuritis" slowly improving with high vitamin diet
H. M.	—	6	2.7	13	Alcoholic neuritis 2 years; no alcohol, fair diet past year, with slow improvement

PERIPHERAL NEUROPATHY OF UNCERTAIN NATURE OR CAUSE

The group in table 8 requires special comment because of the frequent use of the term " neuritis " to describe almost any type of pain or nervous system symptoms. These patients were all carefully examined by the regular staff of either the Neurology or the Neuro-Surgery Departments of the University of California Clinic, and were all considered to have definite disease of the peripheral nervous system without disease of the central nervous system. No patients with tic douloureux were included in this group.

Eight of the 25 patients excreted 4 per cent or less of the test dose, and of these, four experienced definite relief after thiamin feeding. Patient S. F. is particularly interesting. A middle-aged well controlled diabetic, she had been for several years on a well balanced diet and regular insulin. Eighteen months prior to the first test she had developed the habit of drinking large amounts of fluids (no alcohol), and habitually had excreted 4 to 6 liters of urine daily. Nine months later, three months after changing to crystalline insulin, progressively severe paresthesias of the hands began to interfere with her work of packing cookies. Various medications used were

TABLE VIII

Patient With Peripheral Neuritis of Uncertain Nature or Cause

Patient	Diet	Area Involved	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
T. E.	Poor	Neck; arms; pain, hypesthesia	4	0	0	"Scalenus anticus syndrome" unrelieved by operation; general health, but not pain, improved by thiamin orally
A. H.	Poor	Arms, hands; pain, paresthesias	5.0	1.2	7	Pain, paresthesia, anorexia, strength imp. on thiamin
J. S.	?	Sciatic pain	7	1.1	15	Psychosis; no thiamin given
C. B.	Fair	Pain arms and legs	8	1.5	8	Controlled diabetes; pains cured by thiamin 2 mg. thrice daily for 2 weeks
L. O.	Fair	Multiple; pain, anesthesia, contractures	12	2.2 (not based on weight)	43	Followed extraction infected teeth and tonsillitis; not improved by thiamin orally and parenterally
F. E.	Poor last 2 wks. only	Brachial plexus;	8	2.6	14	Recent alcoholic excess to relieve pain; not improved by thiamin
L. R.	Poor	Right arm and leg pain and paresthesias	5	3.6	10	Marked relief pain and general health with thiamin 3 mg. daily orally for 3 weeks
D. B.	Good	Pain arm; tremor	5	3.8	14	Pain and tremor markedly improved on thiamin 3 mg. thrice daily
S. F.	Good	Hands. Marked paresthesias hyperesthesia	5	4.2	4	See below
G. M.	Fair	Arms, back	11	4.6	41	Probable osteo-arthritis. No improvement on thiamin 3 mg. thrice daily
C. L.	Poor	Sciatic pain	5	5.2	14	Multiple neurofibromatosis; general osteo-porosis; no thiamin given
F. P.	Good	Arms, hands; paresthesias; hypesthesia	7	6.1	40	Marked cervical lordosis; no thiamin given
C. A.	Good	Sciatic pain	6	6.4	29	Well controlled diabetes; equivocal relief from thiamin
N. A.	Good	Sciatic pain	9	6.8	29	Mild diabetes; no thiamin given
R. S.	Good	Hands, feet; paresthesias	5	7	32	No relief from oral and parenteral thiamin, B complex, liver, in large doses for one year
J. T.	Fair	Arms; pain, hypesthesia	9	7.1	18	Possibly traumatic; works as lather; no thiamin given
R. B.	Good	Neck, ulnar arm pain, hypesthesia	7	7.2	14	Cervical osteo-arthritis unrelieved by thiamin 3 mg. daily for one month
A. D.	Good	Peroneal, anesthesia	7	7.8	23	Probably traumatic; no thiamin given
B. H.	Good	Supra- and infra-orbital pain	9	7.8	35	Probably caused by sinusitis
B. G.	Fair	Arm pain, hypesthesia	5	8.4	36	"Scalenus anticus syndrome"
L. H.	Good	Facial pain	5	9.2	25	Severe facial neuralgia with hemihypertrophy
F. B.	Excellent	Arms, legs	6	16.7	71	Probably spinal osteo-arthritis
D. S.	Excellent B sup.	Legs, feet	1 4 times daily 5 mos.	23	79	Treated 1 year with large doses thiamin and B complex orally and I.V. without improvement.
B. M.	Good	Acroparesthesia; 6 mos. pregnant	8	9.7	51	No relief from thiamin 3 mg. 4 times daily for three weeks
E. D.	Good	Pain arm	5	9.7	26	No relief from thiamin 2 mg. thrice daily for 3 weeks

ineffective and for seven months she had never been free of the symptoms. On February 2, 1939 she excreted 4.2 per cent of the standard test dose in 5.1 L. of urine. Two mg. of thiamin given three times a day brought *complete* relief within one week. The dose was then reduced to 1 mg. twice daily. On March 6, on the same dosage, she excreted 600 micrograms of thiamin in 4.5 L. of urine (30 per cent). On March 17, the paresthesias recurred, and on April 10 she excreted 1600 micrograms in 4 L. On increasing the dose to 2 mg. thrice daily she again experienced complete relief in five days, and has since (September 1939) been completely free of symptoms. On April 17, the excretion was 2,650 micrograms in 2.7 L.; on May 1, 1500 micrograms in 2.9 L.; on June 1, 2400 micrograms in 3 L.

The diabetes remained under excellent control throughout the period of observation. It is apparent that her requirement for thiamin is much greater than normal. This may be associated in some manner with unknown metabolic disturbances related to the diabetes; it is probable that the diuresis contributed to the relative deficiency. Reference has been made already to the work of Cowgill on the influence of diuresis on the development of thiamin deficiency. Work is in progress to elucidate a possible relationship between the zinc present in crystalline insulin and the thiamin requirement in man.

Patient B. M. presented the problem of progressively severe acroparesthesias beginning in the third month of pregnancy. Until her high excretion was known, she was considered to have thiamin deficiency disease. No relief, however, was obtained from feeding thiamin in doses of 3 mg. thrice daily for three weeks, thus supporting the conclusion drawn from the excretion studies that thiamin deficiency was not the cause of the symptom.

Multiple Sclerosis

Most of these 14 patients (table 9) had severe, well-defined multiple sclerosis. Many were mentally so deteriorated as to make adequate nutrition difficult. In only the first patient was an attempt made to give thiamin in large doses parenterally. Although there appeared to be definite improvement following the injections, the follow-up of this patient has been too short for definite opinion as to the result of the treatment. In some of the patients with low excretions, small doses of thiamin or vitamin B complex by mouth led to improvement in appetite, a sense of well-being, and strength —all compatible with our knowledge of the effects of the vitamin in deficiency states, and not necessarily reflecting change in the primary disease.

Of the 14 patients, seven (50 per cent) excreted less than 4 per cent of the test dose, and four (29 per cent) had some symptomatic improvement from the use of thiamin.

Dorsolateral Sclerosis

As indicated in table 10, the few patients with Addisonian anemia and dorsolateral sclerosis had subnormal excretions with the exception of one

TABLE IX

Patients with Multiple Sclerosis

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/ 100 ml. Urine	Comment
F. T.	Poor food faddist	6	0.5	2	Duration 2 years; severe G. I. symptoms; improved appetite, weight, strength, coordination after 6 injections of 10 mg. thiamin; 1 mo. later symptoms became worse despite use of B complex orally (approx. 2 mg. daily) lost weight; again improved after further injections.
R. J.	Poor	6	1.5	6	Unsteady gait 8 years; severe paresthesias; appetite and strength improved on thiamin 1 mg. thrice daily
C. S.	Poor	6.6	1.6	6	Improved appetite, coördination on thiamin 1 mg. thrice daily
J. T.	Poor	7	2.1	8	Duration 5 years, not severe; no improvement on thiamin 1 mg. thrice daily
L. O.	?	6	2.3(5 hrs.)		Markedly deteriorated; no improvement on thiamin 2 mg. thrice daily
D. K.	?	5	2.3(5 hrs.)		Markedly deteriorated; results of thiamin therapy unknown
F. B.	?	5	2.7	30	Markedly deteriorated; slight improvement strength on thiamin
P. P.	Fair	7	5	35	Duration 1 year; severe paresthesias; effect of thiamin unknown
J. H.	Fair	5	5.8	23	Duration 5 years; markedly deteriorated
E. W.	Fair	6	5.8	27	Effect of thiamin unknown
G. S.	Good	8	8.3	70	Possible slight improvement prior to testing during a year of therapy with liver and B complex
J. R.	Excellent Recent B supplement	9	8.5	39	No improvement with thiamin 3 mg. thrice daily 4 months
W. S.	Good	6	9.4	39	Progressive deterioration while taking thiamin 1 mg. thrice daily 5 months
S. J.	Good yeast supplement recently	7	11.1	97	Progressive disability despite large doses of yeast 1 year

TABLE X

Patients With Dorso-Lateral Sclerosis, Achlorhydria, and Addisonian Anemia

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/ 100 ml. Urine	Comment
J. L. V.	Fair	5	0.4	4	Severe untreated P.A.; classical C.N.S. manifestations
W. A.	Fair	9	3.6	30	Severe untreated P.A., very mild neurological manifestations
J. A.	Fair	6	3.8	22	Moderate anemia; definite neurological disease of moderate severity
H. Y.	Fair: Recent liver therap.	8	8.2	75	Inadequately treated 3 years; neurological manifestations 1 year

patient who had had crude liver extract parenterally within a few days of testing.

Harris et al.[9] have found subnormal excretions of thiamin in several patients with dorsolateral sclerosis, some with and some without anemia. Van der Scheer and Koek [23] found both clinical and histological evidence of peripheral nerve disease in pernicious anemia. It is possible that part of the neurological picture of Addisonian anemia is caused by thiamin deficiency, with functional change in peripheral nerves. This might contribute to the favorable results reported in treatment of dorsolateral sclerosis with synthetic thiamin.

Central Nervous System Syphilis

All patients in this group (table 11) had been receiving the usual treatment for central nervous system syphilis for from six months to five years. In all cases the diagnoses were confirmed by the usual clinical and laboratory tests. Most of the patients were on relief. Allowing for this fact, with its implications of a restricted dietary, there still seemed to be a significant discrepancy between the dietary histories and the states of "saturation" with thiamin as indicated by the excretions. Little is known of the effects of chronic infection on the thiamin requirement, and nothing is known of the effect of heavy metals, which these patients were receiving constantly.

Of the 15 patients, 12 (80 per cent) excreted less than 4 per cent of the test dose. Seven of these had definite improvement in general health, neurological symptoms, or both following oral administration of moderate doses of thiamin. Patients with definite mental deterioration or euphoria were not recorded as "improved," regardless of their statements. There was no obvious relationship between type and duration of antiluetic therapy and improvement on thiamin feeding.

Reese and Hodgson [24] have reported improvement in the neurological status of patients with untreated central nervous system syphilis after administration of vitamin B complex. In many patients of our group, some symptoms that had been attributed simply to the infection were specifically cured by thiamin feeding. This fact and the low excretions found, indicate that thiamin deficiency contributed to the clinical picture.

Tic Douloureux

Patients with facial neuralgias not typically tic douloureux were excluded from this group (table 12). The excretions in this group indicate moderate to mild degrees of deficiency. It is, of course, impossible to assert that this undersaturation is chronic, but dietary histories have indicated no profound recent changes in the diets. Of the nine patients whose excretions were estimated, four excreted less than 4 per cent, six less than 5 per cent, and seven less than 6 per cent.

TABLE XI

Patients With Luetic Disease of the Central Nervous System

Patient	Diagnosis	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
C. B.	Paresis	Unknown	6	0.5	6	Rapid deterioration
C. G.	Tabes, very severe formication and pain, optic atrophy, lassitude	Fair	6.6	0.7	2.5	Striking improvement in paresthesias, facial pain, constipation, general health on thiamin 1 mg. thrice daily 5 weeks. No improvement in vision
D. C.	Tabes; typical hyperventilation alkalosis, psychoneurosis	Poor	6	1.1	5	No improvement with thiamin 6 weeks; paresthesias typically relieved by ammonium chloride
H. H.	Tabo-paresis	Fair	7	1.3	8	Prog. ataxia and mental deterioration on thiamin 1 mg. thrice daily
A. F.	Unclassified; optic atrophy, facial pain (not "trigger")	Fair	6	1.7	8	Facial pain definitely improved on thiamin 1 mg. thrice daily 1 month
P. C.	Tabes; Charcot knee; pains and paresthesias; constipation; urinary retention; anorexia	Poor	6	2.0	10	On thiamin 1 mg. thrice daily 10 weeks, definitely improved weight, strength, defecation and urination, pain and numbness in legs
G. C.	Tabes; hyperventilation alkalosis	Poor	6	2.1	5	Improvement in paresthesia on thiamin; possible psychologic effect
T. H.	Tabes; lightning pains	Fair	7	2.5	18	Improved after pyrotherapy, no thiamin given
L. M.	Tabes; pains; Charcot knee; optic atrophy	Fair	8	2.5	28	No improvement, thiamin 1 to 2 mg. thrice daily for 10 weeks
G. T.	Tabes; aortitis	Unknown	7	3.3	18	Equivocal imp. pains and paresthesias on thiamin 1 mg. thrice daily
A. C.	Tabo-paresis; sciatic pain	Poor	4	3.4	7	Pain markedly imp. on thiamin 1 mg. thrice daily 4 weeks
C. S.	Unclassified; numbness and dysesthesias leg	Fair	6	3.3	19	Imp. gen. health, but not neurol., on 2 mg. thrice daily 3 months
O. S.	Tabes; Charcot knee, severe pain	Good	7	7.3	26	Prog. worse 6 mos.; no thiamin given
J. W.	Tabes; paresthesias; recurrent malaria (therapeutic)	Good	5	7.8	19	No improvement on thiamin 1 mg. thrice daily for 10 weeks
A. H.	Tabes	Good	7	12.5	35	

TABLE XII

TABLE XII

Patients with Tic Douloureux (Trigeminal Neuralgia)

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
C. G., F. 34. Onset October 1937. No relief after caring for focal infection. Alcohol injection never attempted. No long remissions and no long periods of constant pain	Fair	5.4	2.0	22	Thiamin, 3 mg. thrice daily started September 1938. Improvement began in one month, and pain completely gone in 3 months. Discontinued thiamin December, 1938. Attacks recurred March, 1939, and thiamin was resumed immediately. Pain was slightly improved in 5 weeks, completely gone in 3 months. Now free of pain for 4 months. During first period took ammonium chloride as well as thiamin, but in second period took only thiamin
M. B., F. 42. Classical tic 14 years. Relief for 4 years after alcohol injection, ending in present recurrence of 16 months' duration; with no day free of severe attacks. Slight relief from trethylene during attacks	Good	7	2.9	24	May 1939 started thiamin 2 mg. five times a day. In two weeks noted considerable improvement, stating that she had not felt so well for the past 16 months. Three weeks later attacks still well defined, but very mild. No trethylene used after first week of thiamin therapy. Practically free of pain 8 weeks after starting thiamin. Concomitant relief of "neuralgia" in shoulder. No recurrence of facial or shoulder pain within three months.
V. B., M. 53. Duration 8 years. Remissions infrequent and short past 3 years. Almost constant pain past 5 months	Fair	5	3.0	10	Thiamin 3 mg. thrice daily started October 1939
F. K., F. 37. Duration 13 years, with frequent remissions lasting 2 months to 1 year. Last remission for 6 weeks, until 2 weeks ago. Has extensive infection in teeth and sinuses	Poor	5	3.4	12	Thiamin not given pending results of treatment of dental infection. Four months later stated that extraction of teeth was followed by a remission
C. E., M. 62. Duration 11 years. Relieved for 1 year after alcohol injection. Severe recurrence one month ago in June, 1939	Good	6	4.5	15	On thiamin 3 mg. thrice daily. Noted slight improvement in severity within 4 weeks. No further information available as yet
W. C., F. 70. Duration 15 years. Temporary relief twice after alcohol injection. Last attempt at injection failed. Present attack 15 months' duration with almost constant pain and exacerbation set off by trigger mechanism. Also has some residua of hemiplegia that followed cerebral thrombosis (?) 3 years ago	Fair	5	4.8	16	Thiamin 3 mg. thrice daily, started May 1939. After 7 weeks general health markedly improved. Pain still very severe, but altered in character to a burning sensation. In 10 weeks having occasional days free of pain, and severity of pain definitely lessened. After 4 months was free of pain for about 2 weeks, then relatively mild pain recurred only on chewing, after dose of thiamin was reduced to 5 mg. daily

TABLE XII—*Continued*

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
J. R., M. 44. Duration 8 years. Remissions lasting 2 to 8 weeks about twice a year. Remissions shorter past 2 years. Most severe attacks in August every year. Present attack of 8 months' duration. Unsuccessful attempt at alcohol injection December, 1938	Good	7	5.1	24	Thiamin 3 mg. thrice daily. In 2 weeks pain and "trigger" sensitivity less severe. In one month pressure in "trigger" area caused only mild pain. By July 1939, completely free of all but momentary mild twinges of discomfort, hardly to be called pain. No attacks throughout August or September or to the present (October 1939)
I. C., F. 45. Duration about 12 years. Remissions for 1–4 weeks 3 or 4 times a year. Almost constant pain past six months	Fair	5	5.6	55	Thiamin 3 mg. thrice daily. Started September 1939. No further data yet available
M. P., F. 66. Duration 5 years. Remission for 3 months 4 years ago. No long remissions since. Free of pain for total of only 3–5 weeks in past 2 years. Also, has goiter and auricular fibrillation, with moderate dyspnea and palpitation	Good	6	10.6	32	Thiamin 3 mg. thrice daily. Started July 1939. Pain progressively less severe after 2 weeks, and practically free of pain in 5 weeks. No real attacks for 4 weeks (to September 1939). Also noted increase in strength and lessening of dyspnea and palpitation
F. B., F. 64. Duration 8 years. Temporary relief after 10 alcohol injections, one lasting 3 months 3 years ago. Last remission December 1938 for 6 weeks. Almost constant pain since February 1939	Good	—	—	—	Started thiamin 3 mg. thrice daily. Within a week radiation of pain was less extensive. After 2 weeks attacks were shorter. In one month stated that she was "75 per cent better." Former "trigger" zones now devoid of sensitivity. Concomitant increase in general strength, vitality, ambition
W. R., M. 64. Duration 17 years. Used very large amounts of trethylene, with slight relief, for years. Remissions only partial, lasting 1–12 weeks. Last remission lasted 6 weeks, ending 3 months ago. Previous remission lasted 4 weeks one year ago. Used small amounts of vitamin B complex for 7 months (until 9 months ago) with indefinite improvement in severity of attacks	Fair	—	—	—	September 1939 started thiamin 10 mg. subcutaneously and 3 mg. orally daily. 11 days later had sufficient improvement to allow good sleep. Three weeks after beginning thiamin practically free of pain and twitches, and all trigger zones could be prodded with impunity. Now free of symptoms for one month

Because of the irregular course of the disease, one must be very cautious in interpreting the results of treatment, but at present there seems to be ample reason for regarding the effect of thiamin treatment as encouraging. A later complete report will deal with the results in this group of patients after sufficient time has elapsed for an accounting of the probabilities of remissions, etc., as factors involved in the improvement. Borsook and his associates [25] found remarkable and sustained improvement in a large group of patients with this disease. They gave large doses of thiamin parenterally and vitamin B complex by mouth. Most of about 25 per cent of patients not improved subsequently had significant improvement after the administration of large doses of a concentrated liver extract. We have limited our treatment to synthetic thiamin by mouth, hoping to establish the rôle of this substance. The fact that improvement may not begin for several months cannot be adduced as evidence that thiamin is not the effective agent, since it is well known that the curative effect of thiamin may be slow in neuritis definitely attributable to thiamin deficiency that has lasted for a considerable time. If deficiency disease lasts long enough, structural change is superimposed upon the initial functional (chemical) disorder.

Miscellaneous Diseases of the Central Nervous System and Myopathies

This group (table 13) was added simply for comparison. It is of interest that patient J. O. who was considered to have advanced Friedreich's ataxia experienced remarkable improvement in coördination and muscle power after a few months of thiamin feeding, so that he was able to care for himself and even drive a car, formerly beyond his capacity. For a few weeks he also took small amounts of vitamin B complex of unknown nature.

Rheumatoid Arthritis

In general, patients with rheumatoid arthritis (table 14) excreted amounts compatible with their status of "saturation" with thiamin as indicated by dietary history, that is, many of them were undersaturated, as one might expect in any group of the same economic level and food habits. In one patient, M. R., a middle-aged woman with chronic "mucous colitis" who had taken for months a supplement of about 150 I.U. of thiamin daily, the excretion was much lower than might be expected. It is probable that this is related to the diarrhea (see below). No systematic effort was made to study the responses of these patients to thiamin feeding. Of the 24 patients, 11 (46 per cent) had excretions either less than 4 per cent of the test dose or under 50 micrograms without the test dose. Low excretions (under 50 micrograms) were also found in four patients with acute rheumatic fever, not included in the table.

TABLE XIII

Patients With Miscellaneous Diseases of the Central Nervous System: Myopathies

Patient	Diagnosis	Diet	Resting Gamma/ 24 hr.	Dose mg.	Per cent Excreted	Gamma/ 100 ml. Urine	Comment
C. J.	Epilepsy	Fair	—	5	4.8	22	
J. C.	Post-traumatic epilepsy	Good	—	6	8.8	33	
D. H.	Epilepsy	Good	90	5	11	55	Yeast suppl. until 1 week ago
D. R.	Degen. dis. cerebellum with convulsions	Fair	—	2	7.2	18	Equivocal imp. with thiamin 1 mg. thrice daily
M. D.	Lateral sclerosis	Good	170	—	—	—	
R. W.	Amyotrophic lateral sclerosis	Good	—	6	6 (5 hours)	45	Progressively worse on B complex 6 mos.
J. O.	Friedreich's ataxia	Poor	20	7	1.6	20	Definite marked imp. on 2 mg. thiamin thrice daily in 6 mos.
J. S.	Progressive spinal atrophy	Fair	—	7	3.7	30	Slightly better in 3 mos. on B complex
L. T.	Progressive muscular dystrophy	Fair	65	5	7.3	45	No improvement. Thiamin 2 months
J. S.	Myotonia dystrophica	Fair	60	6	4.1	13	
E. A.	Myasthenia gravis	Fair	15	7	3	20	
M. G.	Acetanilid poisoning; prog. degen. cord and possibly periph. nerves	Fair	30	7	6.3	28	No improvement, thiamin and B complex 4 mos., progression of nervous manifestations
F. C.	Chorea major	Fair	59	6	3.4	7	

TABLE XIV

Patients With Active Rheumatoid (Atrophic) Arthritis

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Resting 24 Hours	Comment
M. G.	Poor	—	—	—	40	
E. H.	Poor	—	—	—	32	
O. M.	Poor	—	—	—	44	
C. O.	Good	—	—	—	90	Excellent hospital diet
M. K.	Good	—	—	—	190	Marked fault in absorption of vitamin C
R. R.	Fair	6	1.2	6	10	"Leveled off" at 11.7 per cent
W. F.	Poor	7	1.5	5.5	25	
B. D.	Poor	10	1.8	13	—	
P. T.	Poor	6	2.7	40	25	
M. R.	Good	5	2.9	9	—	Chronic "mucous colitis"; B_1 supplement daily 150 I.U.
R. P.	Poor	6	2.9	8	—	Excretion constant 330 gamma after 1 mg. once daily for 1 month
A. P.	Poor	5	3	16	32	Acute exacerbation, febrile
B. W.	Fair	6	3.4	23	—	Dizziness and weakness attributed to vascular hypertension cleared on 2 mg. thiamin thrice daily 2 weeks
B. M.	Poor	6	3.5	31	0	
H. C.	Fair	8	4.9	26	—	
A. K.	Fair	5	4.4	20	—	
L. H.	Fair	5	4.5	8	—	
T. H.	Fair	6	5	19	—	
C. K.	Fair	7	5.2	21	—	
M. M.	Fair	8	5.5	31	—	
M. S.		5	5.6	25	—	
A. S.	Good	5	5.8	58	—	
F. W.	Fair	5	5.8	24	—	
R. S.	Good	6	6	21	—	
R. C.	Good	5	7.8	11	80	Good hospital diet
A. B.	Good	7	9.9	24	85–130	Good hospital diet
M. W.	Fair	5	10	59	—	
F. G.	Good	4	13.9	50	—	

DISEASE OF THE GASTROINTESTINAL TRACT

In this group (table 15) the most striking findings were in patients with ulcerative colitis, where the excretions were much lower than would be expected from the diets. This conforms to the results obtained experimentally by Dann and Cowgill [26] who showed that absorption of thiamin in dogs was decreased by 20 to 80 per cent by diarrhea produced with magnesium sulfate.

Of great theoretical interest are the excretions in patients with cirrhosis, referred to above, in whom it appears that, probably because of decreased ability of the liver to phosphorylate thiamin for utilization and storage, the excretion is significantly increased.

R. M. provided an example of the effect of thiamin in non-specific diarrhea, recently discussed by Cheney.[27] A middle-aged, rather nervous woman, she had had a distressing diarrhea for about two years. For the past year she had been treated by a gastroenterologist with the usual bland

TABLE XV

Patients With Disease of the Gastrointestinal Tract

Patient	Diagnosis	Diet	Resting Gamma/ 24 hr.	Dose mg.	Per cent Excreted	Gamma/ 100 ml. Urine	Comment
F. A.	Chronic ulcerative colitis, acute relapse	Fair	0; 0; 5	6	1.5	7	Excretion only 2% after 8 test doses
S. S.	Chronic ulcerative colitis, acute relapse	Fair	0	6	0	0	Excretion only 1% after 4 test doses
V. C.	Amebic colitis	Good	—	6	1.1	3	
L. G.	Chronic ulcerative colitis	Fair	18; 7; 6	3	1.6	10	Later excreted 500–700 gamma per 24 hours on suppl. of 600 I.U. daily
L. D.	Chronic ulcerative colitis	Good	10	6	1.3	8	
D. C. (child)	Celiac disease	Good	80; 105	1.5	15	35	Excellent hospital diet
M. C.	"Spastic colon"	Good	—	5	7.2	13	
R. M.	Diarrhea	Poor	—	5	1.3	7	see below
E. P.	Peptic ulcer	Good	95	5	10	21	Milk and cream only for months
N. R.	Peptic ulcer	Fair	30	4	4.9	26	Modified ulcer diet
R. H.	Gastritis	Poor past month	—	5	0.6	5	Gastritis shown by gastroscopy 7 mos. after partial resection for ulcer
O. W.	Gastric carcinoma	Good	—	5	5.1	11	
M. J.	Hematemesis, recurrent; no cause except early cirrhosis found in two laparotomies; neuritis and "beri beri heart" 1 year ago	Poor	—	6.6	0.5	13	Excretion "leveled off" at 15–17% after peak of 25%
M. S.	Cirrhosis; alcoholic; jaundice; neuritis	Poor	—	7.5	0.6	5	Excreted 25% of 10 mg. I.V.
W. B.	Obstructive jaundice	Good	100; 185	7	7.4	35	
A. R.	Obstructive jaundice	Good	75; 110	7	7.9	61	Diet of beans 2 months
A. P.	Cirrhosis, poss. amyloid	Fair	40	5	13	19	"Leveled off" at 19 per cent
M. E.	Obstructive jaundice	Fair	15	5	7.8	37	
M. L.	Cirrhosis	Poor	—	6.6	6.0	100	"Leveled off" at 26%, then dropped to 15%

diet, powders, and atropine. She excreted only 1.3 per cent of the test dose. Thiamin chloride was given in a single dose of 5 mg. daily by mouth, and within 10 days she was having one formed stool daily instead of three to five mushy or liquid stools. At this time she excreted 15.4 per cent of the dose. The dose was then reduced to 1 mg. twice a day, and she has since (for three months) remained free of symptoms. An interesting feature was recovery of the ability to take milk, which had formerly caused severe digestive disturbances.

Level of Excretion at Which Symptoms May Appear

Table 16 presents data bearing upon the "level" of thiamin saturation below which symptoms of deficiency may appear. The patients were selected from the groups noted in the previous tables, with a few additions. The criteria of deficiency (aside from subnormal excretions) were: (1) presence of symptoms that are known to result from thiamin deficiency; and (2) definite relief of symptoms following administration of synthetic thiamin in moderate dosage. Since the manifestations of early or mild thiamin deficiency (as well as other deficiencies) are largely subjective, evaluation of improvement is difficult. Most of these patients had had various medications previously without much effect, and it was believed that psychological factors were thereby minimized.

It is seen that symptoms of thiamin deficiency may occur with excretions as high as 4 per cent of the test dose of 0.1 mg. per kg. of body weight. This observation is generally in agreement with the work of Jolliffe et al.[28] who produced symptoms of thiamin deficiency in human subjects within a few days on low-thiamin diets, and found that thiamin continued to be excreted in significant, though decreased amounts. These findings, coupled with the facts that the major portion of vitamin B_1 in the blood is not in the form of free thiamin [30] and that diuresis may greatly increase the excretion, suggest that thiamin is a non-threshold substance. Unfortunately, there are as yet no good data on the relationship of blood thiamin to urinary thiamin.

It must not be supposed that thiamin feeding will bring about clinical improvement in all patients with any or all of the symptoms noted above, even where low excretions are found. Some of our patients with low excretions were not significantly improved in anorexia, sense of ill health, paresthesias, or constipation by thiamin feeding, and in these it must be supposed that the symptoms had causes other than thiamin deficiency, the latter being only an incidental finding.

On the other hand, several patients with symptoms suggestive of thiamin deficiency disease who had normal excretions were not significantly affected by the giving of a supplement. Such a patient was B.M. (table 8).

TABLE XVI

Levels of Excretion Associated With Symptoms of Deficiency

Patient	Primary Diagnosis	Per cent of Test Dose Excreted	Therapeutic Dose	Symptoms Improved
T. E.	"Scalenus anticus syndrome"	0	1 mg. thrice daily	Anorexia, fatigability
N. J.	Alcoholic neuritis	0.2	3 mg. thrice daily	Anorexia, pain, weakness, paresthesia
R. H.	Alcoholic neuritis	0.3	3 mg. thrice daily	Anorexia, pain, weakness
F. T.	Multiple sclerosis	0.5	10 mg. daily (I.M.)	Anorexia, weakness, acroparesthesias
C. G.	CNS lues	0.7	1 mg. thrice daily	Formications, lassitude, constipation
C. A.	Alcoholic neuritis	0.8	3 mg. thrice daily	Anorexia, pain, paresthesias, weakness
A. H.	Psychoneurosis	1.2	5 mg. I.M. every 2 days	Acroparesthesias, anorexia, weakness
R. M.	Chronic diarrhea	1.3	5 mg. once daily	Diarrhea, sense of ill health
E. W.	Hypertensive cardiovascular disease	1.4	10 mg. twice daily	Weakness, anorexia
F. D.	"Post influenzal" neuritis	1.5	10 mg. thrice daily	Pain, weakness
S. C.	Malnutrition, anemia	1.6	3 mg. thrice daily	Anorexia, weakness, weight loss
A. F.	CNS lues	1.7	1 mg. thrice daily	Anorexia, facial neuralgia, asthenia
C. G.	Tic douloureux	2.0	3 mg. thrice daily	Anorexia, underweight. Sense of ill health
P. O.	CNS lues	2.0	1 mg. thrice daily	Anorexia, weakness, underweight
B. C.	Bronchopneumonia, poor convalescence	2.0	5 mg. once daily	Anorexia, weakness
G. C.	CNS lues	2.1	1 mg. thrice daily	Fatigability, anorexia
M. R.	Tachycardia unknown cause; malnutrition	2.6	0.6 mg. thrice daily	Anorexia, palpitation, general sense of ill health
C. S.	CNS lues	3.3	2 mg. thrice daily	Anorexia, paresthesias; sense of ill health
B. W.	Hypertension, arthritis	3.4	2 mg. thrice daily	Weakness, dizziness
A. C.	CNS lues	3.4	2 mg. thrice daily	Sciatic pain, fatigability
L. R.	Neuritis arm and leg	3.6	2 mg. thrice daily	Pain, anorexia, underweight, lassitude
K. H.	Chronic alcoholic neuritis	3.6	0.6 mg. thrice daily	Paresthesias, weakness
M. P.	Malnutrition	4.6	0.6 mg. thrice daily	Anorexia, underweight, lassitude
W. C.	Tic douloureux	4.8	3 mg. thrice daily	Anorexia, fatigability

Summary and Conclusions

A modification of the thiochrome reaction of Jansen provides an easy, rapid, and accurate method for the chemical assay of thiamin (vitamin B_1) in urine.

Subjects taking a diet known to be adequate in thiamin excrete in the urine from 100 to 300 micrograms daily. Of a standard test dose of 0.1 mg. per kilogram given by mouth 8 to 10 per cent is excreted, most of the excess being found in the first five hours.

The per cent excretion is roughly inversely proportional to the size of the dose given by mouth, and roughly directly proportional to the size of the dose given parenterally. The efficiency of utilization of thiamin supplements depends in part upon the degrees of absorption and excretion, large doses orally being incompletely absorbed and large doses parenterally being rapidly excreted, so that small frequent doses are most efficiently utilized.

The excretion reflects the intake with great sensitivity, even very slight degrees of subsaturation being readily detected. The extent of deficiency may be estimated by determining the number of test doses required for the excretion to rise to normal. In patients with severe thiamin deficiency disease, presumably markedly undersaturated, the total amount required for the excretion to become normal was tentatively estimated at about 100 mg.

Evidence is presented that thiamin is a non-threshold substance. Diuresis may wash out a considerable amount, thus contributing to the development of deficiency.

Data indicating that in diffuse liver disease the excretion may be much higher than normal are interpreted as evidence that the ability to phosphorylate thiamin for utilization and storage is impaired.

Moderate deficiencies were found in patients with thyrotoxicosis despite diets containing fair amounts of "protective foods." This may be explained by the increase in the metabolic rate and the consequent increase in the thiamin requirement, left uncompensated by the addition to the diet of vitamin-poor carbohydrate foods.

In several patients with "neuritis" of uncertain cause significant deficiencies were found. Some of these experienced definite relief after thiamin feeding, indicating that thiamin deficiency played a part in the etiology, although classical thiamin deficiency disease was not present.

Fifty per cent of patients with multiple sclerosis were markedly subsaturated, and 29 per cent had definite symptomatic improvement after administration of thiamin by mouth. It is thought that the deficiency is secondary, there being no evidence that the primary disease was influenced by the treatment.

Deficiencies were frequently found in patients with dorsolateral sclerosis and miscellaneous diseases of the central nervous system.

Eighty per cent of patients with central nervous system syphilis were found to be undersaturated with thiamin. Of these, 58 per cent had definite

improvement in general health or neurological symptoms or both following administration of pure thiamin.

A preliminary report is presented of the effect of thiamin in tic douloureux. There appears to be a definite indication for its use as a therapeutic measure. It is probable that long-continued administration of the vitamin is necessary in some patients before improvement will begin.

Severe deficiencies of thiamin were found in patients with diarrhea, apparently because of inadequate absorption. Thiamin feeding was found to be curative in a patient with non-specific diarrhea, who also recovered from an idiosyncrasy to milk.

Thiamin deficiency is very frequently found in mild degree in patients with chronic disease of various types, and may produce symptoms which are attributed to the primary disease, or to "functional" disorders. Because of the absence of the classical picture of deficiency disease, these can be diagnosed only by the therapeutic test. By estimating the urinary excretion, asymptomatic deficiencies may be readily discovered, and the therapeutic test may be placed upon a sounder basis in diagnosis of deficiencies associated with symptoms.

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VITAMIN DEFICIENCIES IN GASTROINTESTINAL DISEASE *

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No field of internal medicine is attracting more attention nor yielding a more rapid accumulation of important information than the study of the avitaminoses. Until very recently the term vitamin deficiency disease has been restricted to a small group of conditions representing maximal degrees of deprivation including such entities as rickets, scurvy, pellagra, beri beri, sprue, and certain macrocytic anemias. The belief has been widespread therefore that vitamin deficiencies are uncommon if not actually rare.

The changing perspective of the present is directly traceable to the chemical identification and synthesis of many of these specific food factors. This has permitted great broadening of the field of research. Investigation of the pathology of avitaminosis has been supplemented by study of the physiology of the vitamins particularly with reference to their function in cellular metabolism. Chemical and physical tests have been devised which permit quantitative measurements of vitamin concentration in biological materials; and availability of the pure synthetic vitamins has permitted confirmation by the therapeutic test. Finally the hospital ward has been linked to the nutrition laboratory. The fruitfulness of this field is attested by the increasing volume of clinical literature which is associating a great variety of disease conditions with a varied and at times highly significant vitamin deficit.

The number of vitamins known to be required for human nutrition has increased as research has progressed and it is almost certain that others will be added in the future. The vitamins today known to be required by man are A, thiamin, riboflavin, nicotinic acid (amide), B_6, C, D, K and possibly E.

PATHOLOGY OF VITAMIN DEFICIENCY

Present concepts of the pathology of the avitaminoses are, to a large extent, based upon studies of experimental animals subjected to deficient diets. Certain of the changes found in these animals have been observed in man,[1] others have not. The field is new, however, and requires much additional study. The following discussion of the anatomic changes accompanying avitaminoses is based upon the experimental pathology and such confirmatory observations in man as are available. Necessarily it is incomplete.

The maintenance of specialized epithelial structures has been shown to be the primary function of vitamin A. Atrophy followed by metaplasia and

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differentiation into stratified squamous epithelium results from deprivation of this vitamin. These changes occur in the cornea, the conjunctiva, the parocular glands, and the respiratory tract. They have not been demonstrated to occur in the gastrointestinal tract of man. There are characteristic manifestations in the skin. The most striking of these are excessive dryness and scaliness, and the development of keratotic plugs in the hair follicles, the so-called hyperkeratosis follicularis. There is cessation of bone growth due to failure of cartilage differentiation. Osteoid tissue is scanty and both bone and cartilage become densely calcified. The enamel organ of the teeth is affected and imperfect enamel is produced.

Thiamin, vitamin B_1, or the antineuritic vitamin is intimately associated with beri beri, and with certain forms of peripheral neuritis. It has not been proved, however, that deficiency of this vitamin *per se* is responsible for the characteristic pathology. Recently it has been shown that administration of beta carotene or percomorph oil with riboflavin removes all evidence of peripheral nerve pathology in thiamin deficient chicks, and conversely, that neuropathologic changes seldom occur in rats maintained on a diet deficient in thiamin but adequate in other respects.[2] This suggests that the myelin degeneration in human beri beri depends upon factors other than a simple lack of the antineuritic vitamin. Chemical evidence indicates that polyneuritis is a disease characterized by a general disturbance of carbohydrate metabolism, rather than one primarily producing lesions of the nervous system.[3] Advanced grades of thiamin deficiency, however, are accompanied by extensive changes. There is degeneration of the myelin sheaths of peripheral nerves, and vacuolation and liquefaction necrosis of the ganglion cells of the mesencephalon, metencephalon, and the anterior horn cells of the spinal cord.

Our knowledge of the pathology of riboflavin deficiency is almost certainly incomplete. Recently, however, certain definite lesions have been recognized in man.[4, 5] The lips become reddened and shiny with maceration and fissuring at the angles of the mouth. Seborrheic accumulations develop in the naso-labial fold. The tongue becomes clean and purplish red or magenta in color and presents flattened mushroom-shaped papillae. Capillary ingrowth into the cornea occurs. There is interstitial infiltration with exudate, and the development of diffuse or patchy superficial and interstitial corneal opacities. Experimental animals and birds maintained on a riboflavin-deficient diet, exhibit specific lesions. Myelin changes, especially in the main peripheral nerve trunks occur in chicks.[6] A characteristic dermatitis is produced in rats.[7] Excess fat is found in the liver of birds.[8] Dogs present a yellow mottling of the liver and degenerative changes in the central nervous system.[9]

The demonstration that nicotinic acid was curative for experimental "black tongue" in dogs [10] was immediately followed by its application to the problem of human pellagra for which it likewise was found to be curative.[11, 12, 13, 14] Nicotinic acid deficiency therefore, is directly linked to acute

glossitis, stomatitis and enteritis. Characteristic changes occur in the skin especially in those areas exposed to sunlight. Acute dermatitis appears first, followed by pigmentation and atrophy which leaves the skin thin and parchment-like. Similar changes although usually less intense may occur in the peri anal region, the scrotum, vulva, and vagina.

The pathology of vitamin B_6 deficiency has not been established as yet.

Vitamin C, ascorbic acid, has been extensively studied. Lack of this vitamin leads to inability of supporting tissues to produce and to maintain normal inter-cellular matrix. This results in weakening of vascular walls, increased capillary fragility and consequent extravasation of blood. It likewise produces abnormalities of tooth structure in young animals. Odontoblasts are replaced by osteoblasts, bone is produced instead of dentine, and the dental pulp undergoes fibroid degeneration.

The rôle of vitamin D deficiency in the production of pathologic changes in the growing bones of young animals is well proved. A variety of dental defects are demonstrable in experimental animals maintained on a rachitic diet. The teeth erupt late. They are irregularly set. The enamel is of poor quality. And the jaw bone is spongy.

It is probable that it affects human dentition as well. There is clinical evidence that vitamin D plays an important rôle in tooth formation, and the maintenance of normal tooth structure in man. This probability is supported by the demonstration that the mineral content of the teeth is not completely fixed, but subject to constant mobilization and replacement.[15]

The relationship of vitamin E deficiency to human disease is based mainly upon the therapeutic value of this substance in the control of certain cases of habitual abortion and muscular dystrophy. Lack of this vitamin impairs fertility of experimental animals by interference with placental function in the female, and with spermatogenesis in the male.[16]

A second antihemorrhagic factor, vitamin K, has recently been recognized. It is an oil soluble substance which requires the presence of bile salts for absorption from the intestine. This vitamin plays an essential although indirect rôle in the blood clotting mechanism by ensuring a normal supply of pro-thrombin, provided the liver is functionally active. Deficiency of this vitamin by interference with blood clot formation is an important factor in hemorrhage which may be spontaneous and which may be both dangerous and prolonged.

Energy Metabolism and the Vitamins

Until very recently the avitaminoses have been considered only in terms of anatomic pathology. The unfolding of the chemical structure of the vitamins and their synthesis in pure form have opened a new field of research in biochemistry and physiology. Evidence already available demonstrates that the vitamins play an essential rôle in the metabolism of all living cells.[17] Lacking these substances cellular metabolism is impaired and func-

tion altered. Implicit in these facts are possibilities of enormous potential importance in clinical medicine. Furthermore the pathology of vitamin deficiencies is placed in a new perspective. The characteristic lesions of single avitaminoses must be regarded as the anatomic response to extreme deficiency by the most vulnerable tissue, rather than as a complete picture of the effects of the particular deficiency.

Szent-Gyorgyi [18] has stated that whenever nature provides a system offering two potential energy levels and the possibility of energy release, life appears, causes the system to drop to its lower energy level, and utilizes the energy liberated for its own purposes. The sources of this energy for life are to be found in the intra-cellular oxidation and reduction systems of the body. They are two-fold. The union of two atoms of hydrogen with one of oxygen yields 68 calories. Sugar must first be phosphorylated in the process of yielding its energy, and additional energy is released in the formation of phosphoric acid esters.

Liberation of energy, however, must be gradual rather than sudden or explosive which would be destructive to the cell. This is accomplished by three sets of compounds: enzymes (dehydrogenases and phosphatases) which detach hydrogen and phosphoric acid from the food molecule; acceptors which can receive and carry hydrogen, phosphoric acid, and electrons (coenzymes, phosphoric acid esters, cytochromes); and lastly enzymes that activate substances to accept hydrogen, phosphoric acid, and electrons (oxidases, metal proteids). Furthermore, the transport and shift of hydrogen, phosphoric acid, and electrons require the presence of other enzymes and coenzymes such as mutases, carboxylases, and cocarboxylases.

Thiamin, riboflavin, and nicotinic acid amide have been shown to be the chemically active or prosthetic group in many of the enzymes required by the mammalian body. The chemical structure of B_6, E, and K makes it highly probable that they perform a like function. Ascorbic acid by virtue of its capacity for reversible oxidation and reduction is chemically capable of acting as a hydrogen carrier.

The fundamental rôle of the vitamins in the processes of intracellular metabolism may be emphasized by schematic presentation. This is diagrammed in charts 1 and 2. The actual processes of energy release, however, are infinitely more complicated and many of the intermediate steps are still unknown.

The foodstuff molecule, or hydrogen donator, on activation by dehydrogenase yields two atoms of hydrogen to the coenzyme, codehydrogenase, an integral part of which is frequently riboflavin. The hydrogen is then handed on to the chains of hydrogen acceptors through which it passes. Nicotinic acid amide, riboflavin, B_6, E, and K all can function as hydrogen acceptors. Although ascorbic acid is chemically able to act in this way, it has not been proved to do so in the animal body.

At the end of the chain the hydrogen-hydrogen-acceptor complex is re-

duced by a metal yielding a hydrogen ion and an electron. The electron in its turn is passed along a chain of electron carriers, the metal proteids or cytochromes. Finally cytochrome A is oxidized by cytochrome oxidase, integral constituents of which are nicotinic acid amide and B_6. Oxygen enters into this reaction taking up electrons previously given off by hydrogen. After receipt of the electrons, the oxygen reacts with hydrogen ions to form water. The available energy of the hydrogen of the foodstuff is thus progressively liberated by the passage through the chain of hydrogen carriers, and finally by giving up its electron to the electron carrier. The rôle of oxygen is limited to that of an electron acceptor.

CHART I

Biological Oxidation to H_2O

68 Calories

H Donator

H Activation: Foodstuff + { dehydrogenase / codehydrogenase } → 2H + H acceptor; 2H + H acceptor; 2H + H acceptor; 2H + H acceptor } Nicotinic Acid, Riboflavin, B_6, E, K, C?

Chain of H Carriers: Riboflavin

Electron Donator

Reduction: (H + H acceptor) + metal → electron + metal proteid; electron + metal proteid; electron + metal proteid; electron + metal proteid } Cytochromes

H ion

Chain of Electron Carriers:

Electron Acceptor

Oxidation: O_2 + cytochrome oxidase + (electron + Fe proteid) → (O_2 + 4 electrons)

Nicotinic acid amide

B_6

End Products: (O_2 + 4 electrons) + 4H ions → $2H_2O$

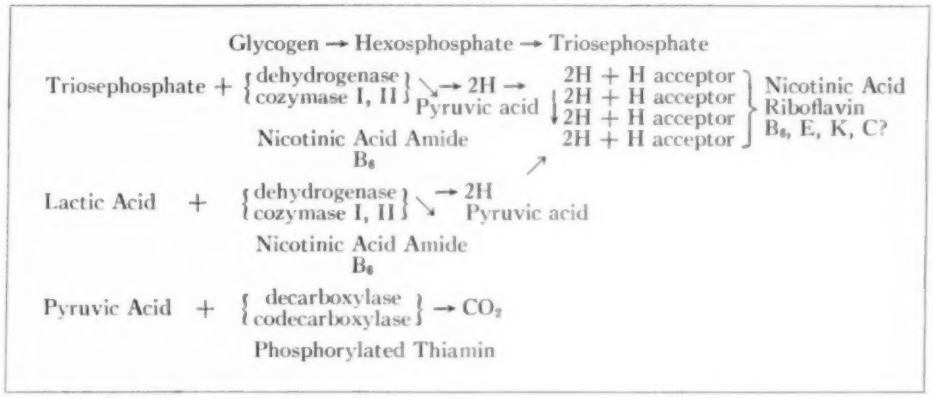
The carbon dioxide formed in the body is not a product of oxidation but is split out of organic acids. It is probable that it is produced by decarboxylation of pyruvic acid, an intermediate product of carbohydrate and fat metabolism. Here again the joint action of enzymes and coenzymes is required. Nicotinic acid, vitamin B_6, and thiamin are essential constituents of certain of these coenzymes.

Chart 2 presents schematically the oxidation of carbohydrate to carbon dioxide. Triosephosphate on activation by a dehydrogenase gives up hydrogen to cozymase. This coenzyme contains nicotinic acid and B_6. Pyruvic acid is formed by this reaction. Lactic acid, an intermediate product in the metabolism of muscle, similarly yields pyruvic acid and hydrogen. The hydrogen for these reactions is passed through the chain of carriers, ultimately to form water as indicated in chart 1. Pyruvic acid, however, in the presence of the enzyme decarboxylase, and the coenzyme codecarboxylase of which phosphorylated thiamin is an integral part, yields acetaldehyde and carbon dioxide.

Vitamin D although apparently playing no direct rôle in these oxidation-reduction reactions plays an important part in cellular energy metabolism by its control of phosphorus availability. The phosphate ion is an essential constituent of many enzymes.

CHART II

Biological Oxidation to CO_2


Glycogen → Hexosphosphate → Triosephosphate
Triosephosphate + dehydrogenase / cozymase I, II → 2H → Pyruvic acid
2H + H acceptor
2H + H acceptor
2H + H acceptor
2H + H acceptor
Nicotinic Acid
Riboflavin
B6, E, K, C?
Nicotinic Acid Amide
B6
Lactic Acid + dehydrogenase / cozymase I, II → 2H → Pyruvic acid
Nicotinic Acid Amide
B6
Pyruvic Acid + decarboxylase / codecarboxylase → CO2
Phosphorylated Thiamin

PHYSIOLOGIC DISTURBANCES IN VITAMIN DEFICIENCY

In view of the fundamental importance of the vitamins in the metabolism of individual cells a variety of physiologic disturbances must accompany avitaminosis. It is to be anticipated that more than one function will be disturbed by deficiency of a single vitamin and that these disturbances will find expression in different physiologic systems within the body. Actually, available evidence confirms this.

In vitamin A deficiency the secretory function of the skin is impaired. The regeneration of the visual purple of the retina is affected and hemeralopia, or night-blindness, results. Reduction of the urea and creatinine clearances with improvement following correction of the avitaminosis has been reported.[19]

Deficiency of thiamin has been related to a variety of physiologic disturbances. Peters and his associates have demonstrated that in the absence of thiamin the breakdown of carbohydrate is impaired at the pyruvic acid level and that this substance accumulates in blood.[20] As the deficiency develops there is a progressive diminution in carbohydrate tolerance and the development of hyperglycemia which precedes the nervous disturbances.[21] The circulatory system becomes embarrassed. Tachycardia, cardiac enlargement, edema, evidence of cardiac failure and alteration in the electrocardiogram, chiefly T-wave changes, occur.[22] Anorexia appears early, and may respond with extraordinary rapidity, even within 24 hours, to adequate dosage. A variety of gastrointestinal abnormalities including achlorhydria, hypomotility, and atonicity have been attributed to lack of thiamin. Final

proof, however, is lacking. Similarly a variety of nervous and emotional disturbances exclusive of the characteristic neuritis, best described as the syndrome of neurasthenia, have been ascribed to thiamin deficiency.

As yet no demonstrable physiologic disturbances in man have been attributed to lack of riboflavin.

Nicotinic acid, however, appears to exert an immediate effect upon the concentration of cozymase in the blood. Low values corrected by the administration of nicotinic acid have been observed both in pellagra and in diabetes mellitus.[23] Certain types of psychosis occurring in the absence of the characteristic phenomena of pellagra likewise appear to depend upon nicotinic acid deficiency.[24]

Vitamin B_6 deficiency appears to be responsible for certain of the muscular and neurologic symptoms of pellagra which do not respond to nicotinic acid or thiamin therapy.[25]

Ascorbic acid is intimately related to the utilization of iron. The anemia of scurvy, though refractory to iron and liver extract, responds to the exhibition of ascorbic acid by marked reticulocytosis and rapid blood regeneration.[26, 27] This vitamin is said to exert an anti-goiterogenic effect by conserving iodine in the body.[28] It is also fairly well established that vitamin C plays some rôle in immunity through its effect upon the complement activity of the serum,[29] and the process of agglutination.[30]

Vitamin D functions to insure maximal utilization of calcium and phosphorus both by reducing excretion and by increasing absorption. The relationship of deficiency of this factor to certain types of tetany is well known. It is probable that the alimentary glycemia, the lowered oxygen consumption, and the muscular weakness of rickets may all be explained by the disturbed phosphate metabolism.

In view of the varied effects of vitamin deprivation upon normal physiology it is not unexpected that while avitaminosis remains at the level of disturbed physiology, the resulting clinical phenomena will be diverse, atypical of any definite disease entity, and accompanied by few if any physical signs. Certain accompanying symptoms, however, are suggestive. In the presence of more advanced deficiency disease when anatomic changes have appeared diagnosis is often simple. The major symptoms and signs of vitamin deficiency disease are presented in table 1.

What evidence is there that avitaminosis is other than a medical curiosity? The suspicion is growing that the average American dietary is at least suboptimal. The average protein intake is said to have decreased from 100 grams to from 50 to 60 grams per diem in a generation.[31]

Thirty per cent of this is obtained from wheat, a protein which is biologically incomplete. Approximately one-fifth of the total caloric value of the diet is derived from sugar, and four-fifths from foods which have lost much of their vitamin content in various refining processes.

Nutritional surveys indicate that defective diets are demonstrable only in the low income groups.[32] The Council on Pharmacy and Chemistry and the

Council on Foods of the American Medical Association have stated that "—with the exception of pellagra and a possible vitamin B_1 deficiency there is no evidence of a noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a lack of one or more vitamins." [33] They suggest, however, that the optimal diet should contain more vitamin A, thiamin, ascorbic acid and in certain areas more riboflavin and nicotinic acid. It is probable that vitamin D should also be included in this list.

Evaluation of dietary adequacy even for the healthy individual is subject to error. The actual daily requirements for the particular vitamins are unknown. The recommended amounts are based upon assumed minima to which an assumed amount is added as a factor of safety. These recommended amounts from time to time are being increased. Thus from 40 to 60 milligrams of ascorbic acid have been considered an adequate daily allowance.[34] Recently, however, Ralli [35] and her coworkers have found that tissue saturation can be maintained only on a daily intake of at least 100 milligrams. Nutritional surveys based on diet evaluation are estimated from average values of "as purchased" foods and not on the "as served" foods. They do not consider sufficiently the actual individual intake nor the methods of preparation which may produce considerable loss or destruction of the natural vitamin content. Thus cooking with soda, cooking in excess water which is discarded, home canning, pasteurization of milk, and certain methods of preparing meats result in large loss or even complete destruction of at least ascorbic acid and thiamin. There is therefore perhaps a greater weight of

TABLE I

Symptoms and Signs of Vitamin Deficiency

Vitamin	Symptoms	Signs
A	Night blindness	Dry scaly skin Follicular hyperkeratosis Bitots spots
Thiamin B_1	Anorexia Peripheral neuritis Cardiac failure	Muscle tenderness Hyperreflexia—areflexia Diminished vibratory sense Tachycardia
Riboflavin	?	Cheilosis Seborrheic dermatitis Glossitis Keratitis ?
Nicotinic Acid	Painful mouth and tongue Diarrhea, dermatitis Psychosis, stupor	Inflamed, denuded tongue Dermatitis, symmetrical, scrotal, vulval, peri anal
B_6	Weakness, insomnia, nervousness (?)	?
Ascorbic Acid C	Bleeding Pain	Petechiae Spontaneous hemorrhage
D	Rickets Weakness	Cessation of bone growth Disturbed Ca -P metabolism Osteoporosis ?
E	Habitual abortion ?	Muscular dystrophy ?
K	Bleeding	Petechiae Spontaneous hemorrhage

evidence to indicate that the average diet is deficient than that it is adequate. The comparative rarity of gross deficiency disease is not a valid argument that deficiencies at the physiologic level do not exist.

The development of technics for vitamin determination in blood and urine is progressing rapidly. Certain of these are relatively dependable, particularly those for vitamin A, carotene, ascorbic acid, and vitamin K.

Application of these methods to clinical investigation is indicating a far higher incidence of vitamin deficiencies than has been suspected hitherto. The physiologic states of pregnancy and lactation are accompanied by increased requirements for mineral salts and for vitamins. Continued fever produces an increased utilization or loss of ascorbic acid and a raised requirement in comparison with the healthy individual. Deficiencies of this vitamin have been observed in a variety of medical conditions and in postoperative surgical cases. In the evaluation of reports of this type it is important to keep in mind the probability that when one deficiency is demonstrable others are almost certainly present.

Vitamin deficiency states are becoming increasingly important in disorders of the gastrointestinal tract. They may occur from various causes. Conditions such as sprue and extensive regional enteritis are accompanied by defective absorption. Multiple intestinal fistulae and gastro-colic and gastro-jejuno-colic fistula by short-circuiting the intestinal contents prevent normal utilization of diet. Obstructive jaundice or biliary fistula, by exclusion of bile salts from the intestine, condition both vitamin K and vitamin A deficiencies. Intrinsic disease of the liver may likewise be an important factor in the etiology of avitaminosis. Hypermotile diarrheas, in theory at least, also contribute to the development of deficiency by too rapid elimination of the food substrate. The deficiency states occurring in these conditions are termed secondary or conditioned.

The designation primary is reserved for those deficiencies which develop as the result of defective diet. These are not uncommon. They may be exceedingly important. So-called gastrointestinal diets are traditionally oversupplied with starches and sugars. The fruits and green vegetables are proportionally diminished. Functional disorders of the gastrointestinal tract are frequently related to insufficient supplies of the vitamin B complex.[36] In such circumstances restriction to certain of the therapeutic diets will have an additive effect and may precipitate serious deficiency disease. Clinical observations indicate that these deficiency states are accompanied by changes in the small intestine analogous to those which occur in sprue,[37, 38] a condition known to be characterized by impaired absorption. In consequence a vicious ascending spiral may be produced.

We have previously reported the occurrence and importance of mixed deficiency states in chronic ulcerative colitis.[39, 40] More recently we have discussed the value of quantitative estimations of blood vitamin A, carotene, ascorbic acid, and prothrombin time.[41] These studies have been continued with particular reference to cases of peptic ulcer and chronic ulcerative colitis

under treatment in the hospital. The detailed data will be presented subsequently.

Determination of the vitamin A, carotene, and ascorbic acid content of the fasting blood have been made on 51 cases of peptic ulcer on admission and at discharge after standard ulcer therapy.

The admission values for these vitamins were definitely below those of the normal controls and the difference is statistically significant. The discharge values are likewise below those of the controls and the differences are also statistically significant. The limited rise of the mean ascorbic acid value under treatment appears primarily to be due to lack of adequate vitamin C in the diet. However, there is evidence to suggest that defective absorption or utilization plays some part.

TABLE II

Vitamin A

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	39	48	49	61
Mean	2.06 LBU*	1.5 LBU	1.4 LBU	1.46 LBU
Times probable error of difference		9×	9×	7×

* Lovibond blue units per 100 c.c.

Carotene

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	38	50	49	61
Mean	0.75 LYU*	0.63 LYU	0.49 LYU	0.75 LYU
Times probable error of difference		2.4×	6.5×	0

* Lovibond yellow units per 100 c.c.

Ascorbic Acid

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	42	51	51	63
Mean	0.76 mg.*	0.5 mg.	0.61 mg.	0.64 mg.
Times probable error of difference		6×	3×	2.5×

* Milligrams per 100 c.c.

Comparison of the vitamin A values before and after treatment reveals an actual fall of the mean. It is impossible to explain this finding on the grounds of dietary inadequacy. The diet supplied optimal amounts of vitamin A at all times according to present standards. This strongly suggests imperfect absorption. The greater fall of the mean carotene value is not unexpected in view of the limited amounts of green vegetables supplied by the diets. The lack of correlation between the blood A and carotene levels is in keeping with the findings of others.

Similar studies were made of 63 cases of chronic ulcerative colitis when they first came under our observation. The mean blood A and ascorbic acid values are below those of the control group. The differences between the

groups are statistically significant. The mean carotene values, however, were identical.

The disproportion between the levels of blood A and carotene in the controls and in the colitis cases suggests a metabolic defect in the translation of the provitamin carotene to vitamin A. The low ascorbic acid values observed in many of these patients were due to grossly deficient diets, and frequently were associated with severe bleeding from the inflamed colon. Defective absorption, however, appeared to be a factor in at least some of the vitamin A deficiencies. Failure to respond to large oral doses of this vitamin in the form of fish liver oil was common. However, when cod liver oil was administered by inunction prompt and satisfactory rise of the blood A was usually obtained.

The prothrombin time of Quick [42] has been used to determine the vitamin K status in 73 miscellaneous non-jaundiced patients. Twenty-two of these have had elevated prothrombin times. The detailed data will be presented subsequently.

TABLE III

Vitamin K Deficiency without Jaundice

Ulcerative colitis	18 cases
Regional enteritis	2 cases
Tropical sprue	1 case
Banti's disease	1 case

In certain instances this deficiency has been associated with a grossly defective diet and has responded to dietary measures alone. The case of Banti's disease developed a marked elevation of prothrombin time in the course of starvation and limited diet therapy for gastric hemorrhage. It promptly fell to the normal level on resumption of more liberal diet. Similarly the patient with sprue developed a considerably elevated prothrombin time in the postoperative period following surgical intervention for intestinal obstruction. Again return to adequate diet was followed by fall of the prothrombin time to normal. Likewise several of the cases of ulcerative colitis fall into this category.

Our observations indicate, therefore, that jaundice is not a necessary concomitant of vitamin K deficiency and that this complication may constitute part of a mixed vitamin deficiency syndrome. In view of the conditions in which it has been observed the precipitating factors appear to be a chronic disease of the gastrointestinal tract to which is added the effect of starvation, defective diet, poor absorption, or a hypothetical qualitative or quantitative defect of bile secretion.

It is axiomatic that recognition of a vitamin deficiency calls for immediate treatment. This may be accomplished by diet alone, or by diet and supplemental vitamin therapy. In the presence of acute deficiency the latter regime should be used. If the indications for specific vitamin administration exist ample dosage should be used as indicated in table 4.

However, too much dependence must not be placed upon the use of the

purified vitamins, to the neglect of careful dietetics. It is still impossible to keep an experimental animal alive on a vitamin-free food mixture to which have been added ample amounts of all the presently known purified vitamins. Diet still remains the major weapon to combat deficiency disease. It is often advisable to supplement it with crude sources such as Brewer's yeast or unrefined liver extract in large amounts. The purified vitamins should be used as an additional form of therapy to meet special and usually temporary indications.

TABLE IV

Vitamin Therapeutic Dosage

Vitamin A	35,000–100,000	U.S.P. Units per day
Thiamin chloride	20–30	mg. per day
Riboflavin	5	mg. per day
Nicotinic acid	250–500	mg. per day
Vitamin B_6	50	mg. per day
Ascorbic acid	500– 1,000	mg. per day
Vitamin D	1,200– 60,000	U.S.P. Units per day
Vitamin K	1	mg. per day

SUMMARY

The concept of vitamin deficiency disease is being rapidly and radically revised as the result of research in biochemistry. Various of the vitamins have been shown to be the active or prosthetic fractions of enzymes which are essential for the breakdown of foodstuff in intracellular metabolism. They have likewise been shown to have chemical structures which permit them to function in the transfer of hydrogen and phosphorus by which the energy of food is progressively liberated for the use of the individual cell. As this mechanism has been uncovered a variety of metabolic and physiologic disturbances have been associated with the avitaminoses. These are directly traceable to interference with cellular oxidation-reduction systems.

This advance in biochemical knowledge places the problem of the vitamin deficiencies in a new perspective. It is immediately apparent that a vitamin deficiency may exist at two levels. The first is the level of disturbed physiology accompanying the early stages of interference with the chemical processes of the cells. Symptoms may be produced and certain disturbances of normal body chemistry may be demonstrable. Physical signs which depend upon structural alteration, will be absent. However, when the deficiency becomes more intense or of longer duration the level of anatomic change is reached and the classic signs of deficiency disease become evident. Such a concept reconciles the apparently opposed views of those who suspect that vitamin deficiencies are more prevalent than are generally believed, and the view that they are absent because gross deficiency disease is rare.

The function of the stomach and intestinal tract with the accessory organs in the digestion and absorption of food place this system in a position of great importance with respect to the etiology of vitamin deficiencies. Any pathologic condition which interferes with normal food intake, normal di-

gestion, normal absorption of the products of digestion, and normal utilization of these products by the liver, may produce secondary or conditioned avitaminoses.

Primary deficiencies due to defective diet are probably not rare. Many of the dietary regimes in vogue for the treatment of diseases of this system are open to grave suspicion. Our observations of the levels of blood vitamin A, carotene, ascorbic acid, and prothrombin time, demonstrate that diets widely used in the treatment of peptic ulcer and ulcerative colitis are not adequate to maintain normal nutrition.

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THE RELATION BETWEEN CLINICAL EDEMA AND THE EXCRETION OF AN ANTIDIURETIC SUBSTANCE IN THE URINE*

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STARLING's hypothesis relating the exchange of fluid between the capillaries and the interstitial body fluids to a balance between hydrostatic pressure within the capillaries and osmotic pressure of the plasma proteins, permits prediction of some conditions under which edema will be found. Moore and Van Slyke [1] found that in adults with Bright's disease when the plasma albumin level fell below 2.5 grams per 100 c.c. edema almost invariably occurred and could not be controlled by salt restriction alone. Farr and Van Slyke [2] found that in similar circumstances the plasma albumin of children averaged 1.2 grams per 100 c.c. Direct measurements of colloidal osmotic pressures in the sera of these patients by Bourdillon [3] showed the pressures to be in the range expected from the plasma protein concentrations. It may be accepted as established by both physiological experiments and clinical observation that diminution of colloidal osmotic pressure in the plasma is an important factor in producing edema, and that the albumin is the plasma constituent of most importance in maintaining the pressure.[4]

However, clinical edema is not infrequently encountered which cannot be explained on this basis. The edema in acute nephritis frequently is not associated with hypoproteinemia, and there may be no evidence of increase of hydrostatic pressure within the capillaries. Likewise in edema regularly recurring during the menstrual cycle, and in certain endocrine diseases as Cushing's syndrome, the observed variations in extracellular fluid volume cannot be explained on the basis of Starling's theory. Fluctuating edema in patients with the nephrotic syndrome occurs not infrequently on a very low salt intake without associated changes in the level of the plasma proteins.

It appears that at least one factor other than plasma protein content and hydrostatic pressure is concerned with edema formation in patients on limited salt intakes. We have, in this clinic for a number of years, called this the "X-factor" in edema formation, but no suitable laboratory means of detecting the presence or absence of this factor have previously been available.

In 1937 Gilman and Goodman [5] reported that the urine of dehydrated rats showed an antidiuretic activity roughly proportional to the severity of dehydration when tested by the rat assay method of Burn.[6] We have applied their method with slight modifications in the study of the presence or

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absence of an antidiuretic factor in the urine of patients and sought to correlate the presence of this factor with the presence of edema in patients.

Methods

A 24-hour urine specimen was collected in a clean, sterile bottle and acidified with 2 per cent acetic acid. The entire specimen was placed in cellophane tubes of about 2 centimeters in diameter and about 1 meter in length and suspended in the draft of electric fans. This simple and rapid method for concentration used by Van Slyke, Hastings, Hiller and Sendroy[7] has been refined recently by Thalhimer.[8] The urine was concentrated to an approximate volume of 80 c.c. and then dialyzed. Dialysis was carried out by placing an ordinary glass marble in the cellophane tube containing the concentrated urine, tying off tightly the open end to form a waterproof sack, cutting off the excess cellophane tubing, and placing inside a glass tube 5 centimeters in diameter and 30 centimeters in length. Through this tube a constant stream of tap water flowed while the tube was slowly oscillated through a 30 degree angle longitudinally by a shaking apparatus. Oscillating dialysis was continued for 6 to 8 hours to insure complete removal of urea and salts. The dialyzed and concentrated 24-hour urine specimen was then made up to a volume of 100 c.c.; thereby, each 1 c.c. represented the amount of urine excreted in 15 minutes and this amount was used as the standard bioassay dose.

Each bioassay employed 20 rats, two in each of ten cages after an overnight fast. At 9 a.m. each rat was given 2.5 per cent of its body weight in water by gavage and at 11:30 a.m. 5 per cent of its body weight in water by gavage followed by 1 c.c. of the dialyzed concentrate intraperitoneally. The volume of urine excreted by each cage of rats was then measured at 15-minute intervals starting at the time the intraperitoneal injection had been made. Observations were discontinued when the urine volume of each cage equalled 2.5 per cent of the sum of the initial body weights of the rats therein. The period of time required to attain this volume was called the excretion time. When all tests were completed the average excretion time for the ten cages was calculated and this value constituted the bioassay value for that test run. Whenever possible urines for assay were collected on consecutive days and tested with different groups of rats to diminish the effect of biological variations. The same animals were not used more than once a week and after four weeks were discarded and new animals substituted.

Clinical Studies, Experimental Procedure

The patients studied were observed in the hospital or ambulatory clinic. Two patients (D. R. and R. B.) had acute hemorrhagic Bright's disease, and two (A. R. and T. H.) had manifestations of acute hemorrhagic Bright's disease with severe renal failure following treatment of pneumonia with

sulfapyridine. These four patients had well developed edema during the acute manifestations of nephritis and had normal plasma proteins throughout. All made a recovery from their disease or complications.

Three patients, two adults (W. H. and A. T.) and one child (S. W.) had the nephrotic syndrome with well marked hypoproteinemia, edema, and varying degrees of renal insufficiency. In each of these patients we observed spontaneous changes in edema unaccompanied by significant changes in the plasma proteins.

In three patients with the nephrotic syndrome the effect of daily administration of pitressin for one week was observed.

One patient had marked recurrent premenstrual edema. At this time her weight gain amounted to from 2 to 8 kilograms. Her plasma proteins were normal and otherwise she appeared to be normal. This patient was also given pitressin for six days and her urine studied during this interval.

Three patients had diabetes insipidus. Their blood chemistry and urea clearance were normal.

Two patients * had Cushing's syndrome with normal plasma proteins; urea clearance within the lower limit of normal and intermittent edema. Measurements of venous pressures were within normal limits.

In addition, numerous single observations were made on nephrotic patients currently in the hospital, and 11 apparently healthy members of the hospital and laboratory technical staffs were used for normal control observations. Twenty-four hour urine specimens were collected from this group of patients at irregular intervals. No limitations of fluid intake, diet or activity were enforced during periods of urine collection.

Results

Serial tests on several of our patients could not be run because of toxicity of the urine concentrate. On several occasions urine obtained from a patient which previously had been satisfactory would kill all of the rats injected. We were not able to relate this toxic effect to the patient's disease, clinical condition, or to previous injections of the rats. Undoubtedly a varying amount of this toxic material was usually present in the urine as it was not uncommon to lose one or two of 60 rats. Some of the variations in individual tests may have been due to this factor. The urines used were freshly obtained and it was unlikely that the toxic factor resulted from changes occurring subsequent to voiding.

The average time required for the rats to excrete the arbitrary urine volumes after the animals were injected with material obtained from normal individuals was 142 minutes, the standard deviation was $\pm$ 12 minutes. The normal range was obtained by assuming that 2.66 times the standard

* We are indebted to Dr. Ephraim Shorr of the New York Hospital for the opportunity to study two of his patients, one with diabetes insipidus and one with Cushing's syndrome.

deviation provided an adequate margin for biological variation. This range and the actual determinations are shown in figure 1.

The two patients (D. R. and R. B.) with acute hemorrhagic Bright's disease, had a significant amount of the antidiuretic material in their urines when they were edematous. After loss of edema the urine from one of the patients (R. B.) had less than the expected normal average diuretic effect (figure 2). The urines from the two patients (A. R. and T. H.) with nephritis following sulfapyridine therapy of pneumonia, showed a marked antidiuretic effect at the time they had edema (figure 2).

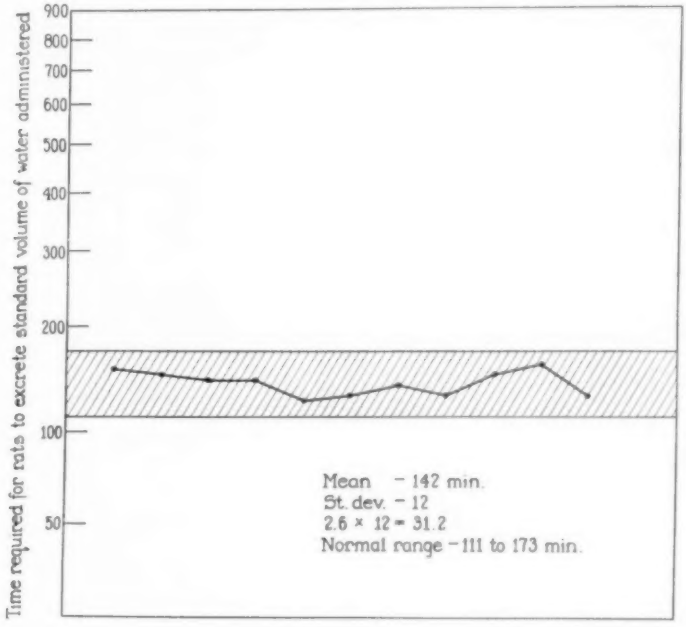

FIG. 1. The antidiuretic titer of urines from 11 normal individuals. The figures on the left represent minutes after administration of the second gavage and intraperitoneal injection of the urine concentrate. The normal range is shown by the shaded area.

The urine from hypoproteinemic, edematous patients with the nephrotic syndrome almost uniformly contained considerable quantities of the antidiuretic material. Spontaneous changes in edema without plasma protein changes were seen in three of these patients. The comparisons of their tests before and after edema loss are shown in figures 3, 4 and 5. The urine from S. W. tested frequently over a two-month period showed no consistent trend over this interval though her weight was steadily decreasing (figure 3). At the beginning of this two-month interval the patient had pitting edema over the sacrum and lower extremities. During this time the antidiuretic effect of the urine was marked. After about two weeks she began gradually to lose her edema and at the end of the two months was apparently edema-free.

There had been no increase in her plasma proteins. On two occasions during the time of edema loss, the antidiuretic effect of her urine was within the normal range. At the end of the two-month period the patient's plasma albumin had fallen from 1.17 to 1.05 grams per 100 c.c. and the antidiuretic effect of her urine had returned to a maximum. Subsequently she regained her edema in part with no change in the antidiuretic quality of the urine. In this instance there was no clear parallel between the urine assay and the patient's clinical condition. The same variability was found in the urine assays on W. H. during a period of edema (figure 4). However, with the

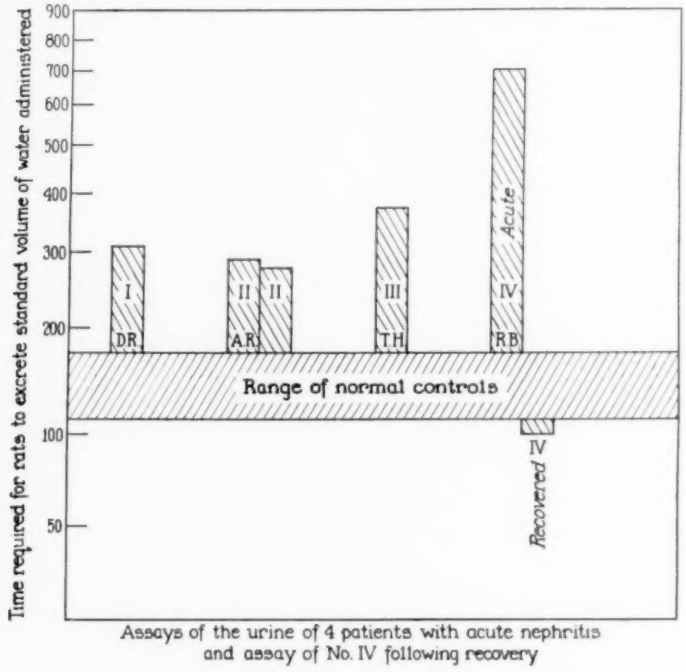

FIG. 2. The assay of 4 patients with edema and nephritis without hypoproteinemia are shown by the height of the vertical columns. Assays on R. B. while edematous and after recovery are shown. D. R. and R. B. had acute hemorrhagic Bright's disease. T. H. and A. R. had manifestations of acute nephritis with edema following sulfapyridine therapy of pneumonia. The time is in minutes.

loss of 17 kilograms of edema the assay of this patient dropped to just outside the normal range and she went for several months edema-free with no change in her plasma proteins. In A. T. the presence of antidiuretic material in the urine correlated closely with the presence of demonstrable edema (figure 5).

The two patients with Cushing's syndrome frequently excreted urine with a marked antidiuretic effect (figures 6 and 7). The initia' loss of edema by L. M. was paralleled by a decrease in antidiuretic titer of her urine

but a subsequent increase in the quantity of antidiuretic material in the urine was not accompanied by edema. Amelioration of some of the symptoms of the disease by continuous estrogenic therapy may have complicated the test during a part of the time as subsequently the patient's edema recurred on several occasions when estrogenic therapy was discontinued.

The urine of the patient with menstrual edema showed only a moderate antidiuretic effect during the edematous period but during the intermenstrual non-edematous interval had no antidiuretic effect whatever.

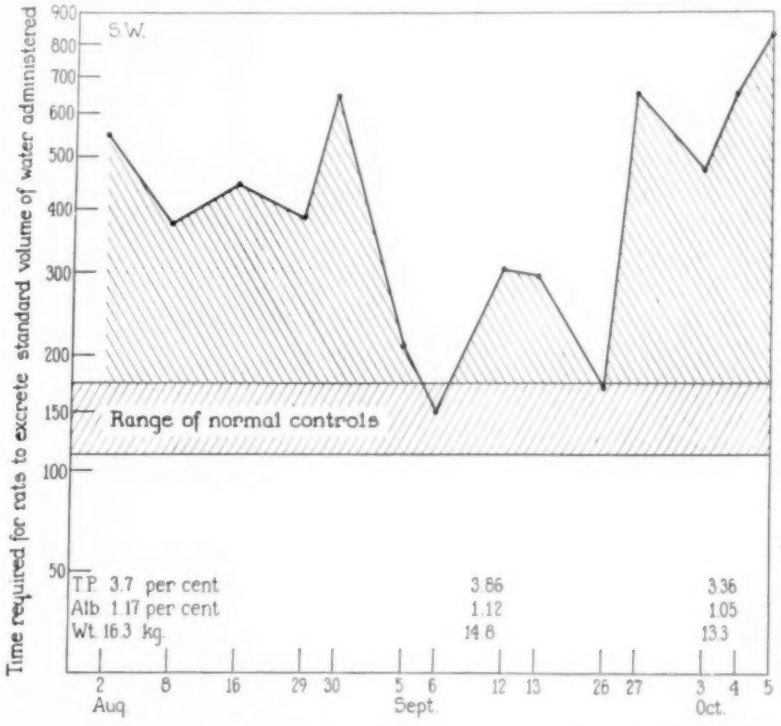

FIG. 3. The assay of S. W., a child with the nephrotic syndrome. This patient lost edema steadily throughout August and September. The plasma proteins also tended to fall. Two assays fell within the normal range but all others were significantly antidiuretic. There was no clinical explanation for lack of correlation between edema loss and antidiuretic titer of the urine. The time is in minutes.

Daily administration for seven days of 30 units of pitressin to four patients was accompanied initially by sharp increases in antidiuretic titer of the urines. This was observed both in patients with antidiuretic and normal urine before pitressin administration. With continued pitressin administration there was a decreased antidiuretic effect from the urine. After four to five days no antidiuretic material in the urine of any of the patients could be demonstrated even though pitressin administrations were continued (figures 8 and 9). The disappearance of antidiuretic material from the urine

paralleled the loss of edema acquired after beginning pitressin administration. No further diuresis occurred in any of our nephrotic patients so treated even though the rat assay fell well below the normal range.

The urine from three patients with diabetes insipidus showed no antidiuretic effect in rats. On the other hand, it did not show any diuretic effect similar to that noted in our patients after pitressin administration.

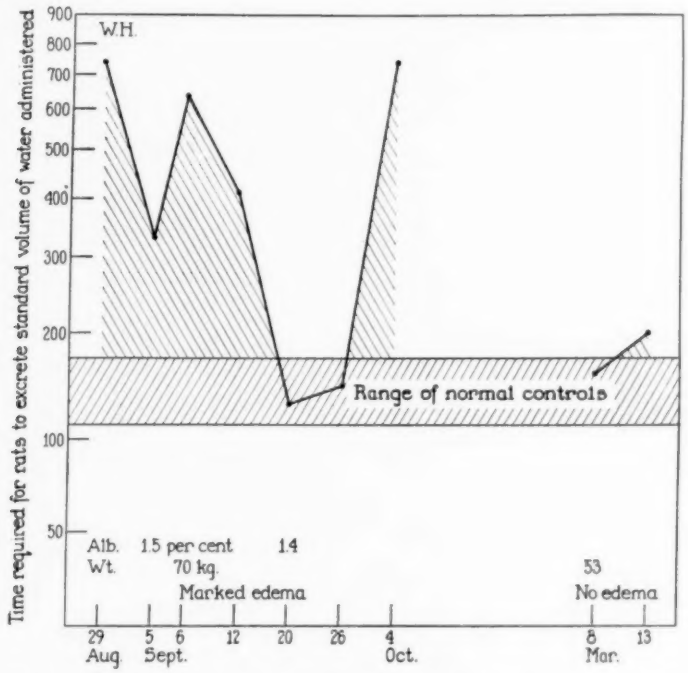

FIG. 4. The assay of W. H. during edematous and non-edematous periods. The two normal values obtained during the period of edema could not be explained on the basis of abrupt clinical changes or laboratory findings. The time is in minutes.

DISCUSSION

One of the most constant results we obtained was the rapid decrease in antidiuretic effect of the urine while the patient was under continuous pitressin administration. The paradoxical induction of diuresis by pitressin administration was previously noted by McQuarrie, Thompson and Ziegler [9] and suggested as a possible treatment of nephrotic edema. It would appear that the patients either destroy pitressin so administered and in so doing decrease the amount normally available to the body, or that they elaborate a physiological antagonist very rapidly. The marked diuretic effect of urine after six days of pitressin administration would favor the latter hypothesis. We have no explanation for the fact that in our nephrotic patients diuresis was sufficient only to remove water retained under the influence of pitressin and did not affect edema fluid previously present.

Teel and Reid,[10] in a recent study of the urine from women who were normally pregnant and those with preëclampsia and eclampsia, found that in the women with toxemia a large majority produced urine containing considerable antidiuretic activity. Although they were interested in relating the results of the bioassays to the presence of toxemia of pregnancy, they stated that the results paralleled only the presence of edema and could not be corre-

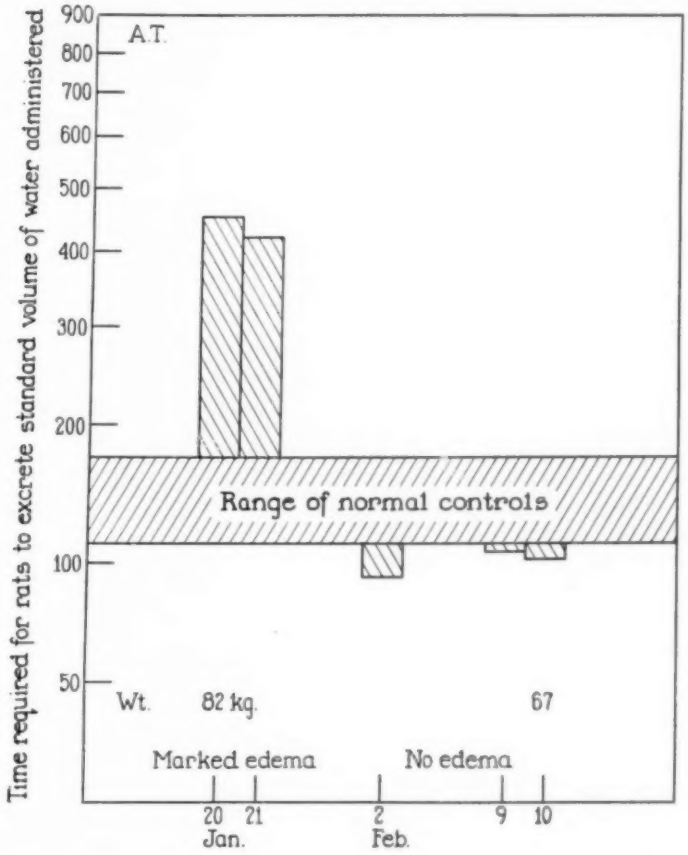

FIG. 5. The antidiuretic values of A. T. correlated with presence or absence of edema. There was no significant change in the patient's plasma proteins during this period of edema loss. The time is in minutes.

lated with albuminuria or hypertension. They found, as have we, that some patients with edema showed no increased antidiuretic titer in the urine, and the urine from an occasional non-edematous patient showed an antidiuretic effect outside of the normal expected range. They carried out studies of the adsorption of the material by urine protein and stated that otherwise potent urine might be rendered inactive due to adsorption of the

principle on protein which in their technic was removed. We found that in our patients the activity persisted without removal of protein. Teel and Reid made no statement of toxic effects from the urine such as we encountered. We were unable to remove the toxic factor by removal of the proteins in one attempt.

Although Teel and Reid [10] in their study in humans, and Ingram, Ladd and Benbow [11] in a study of cats, interpret their results as offering support for the suggestion of Gilman and Goodman that the antidiuretic factor in the urine is derived from the neurohypophysis, Walker [12] has brought forth evi-

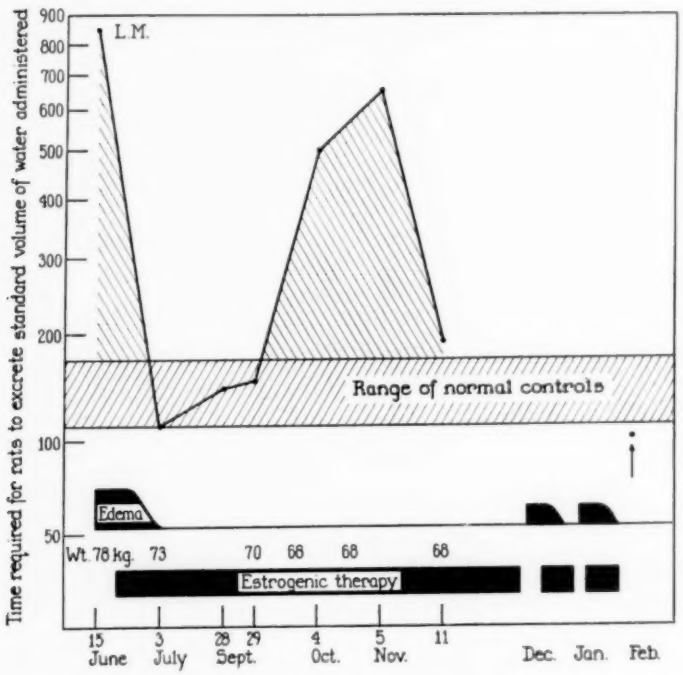

FIG. 6. The initial loss of antidiuretic potency in the urine of L.M. correlated with loss of edema. Intensive estrogenic therapy subsequently instituted may have altered the usual response as on two occasions edema returned when estrogenic therapy was suspended. One assay done in February, when the patient was edema-free and was not receiving estrogenic therapy, showed a value below the expected range. The time is in minutes.

dence that this is not likely. He used not only the rat assay method of Burn but also a very sensitive rabbit assay method which he devised. He failed to find any definite support for the pituitary theory of water diuresis. He was, however, able to confirm the finding of an antidiuretic substance in the urine of dehydrated animals when the method of Gilman and Goodman was used throughout.

Very recently Hare [13] has reported work of significance in regard to the nature of the antidiuretic substance. Hare used dogs with surgically in-

duced diabetes insipidus as his test animals. In these animals the diabetes insipidus could be controlled very satisfactorily by the use of pitression. Hare used as his test, not simple urine excretion but changes in the creatinine

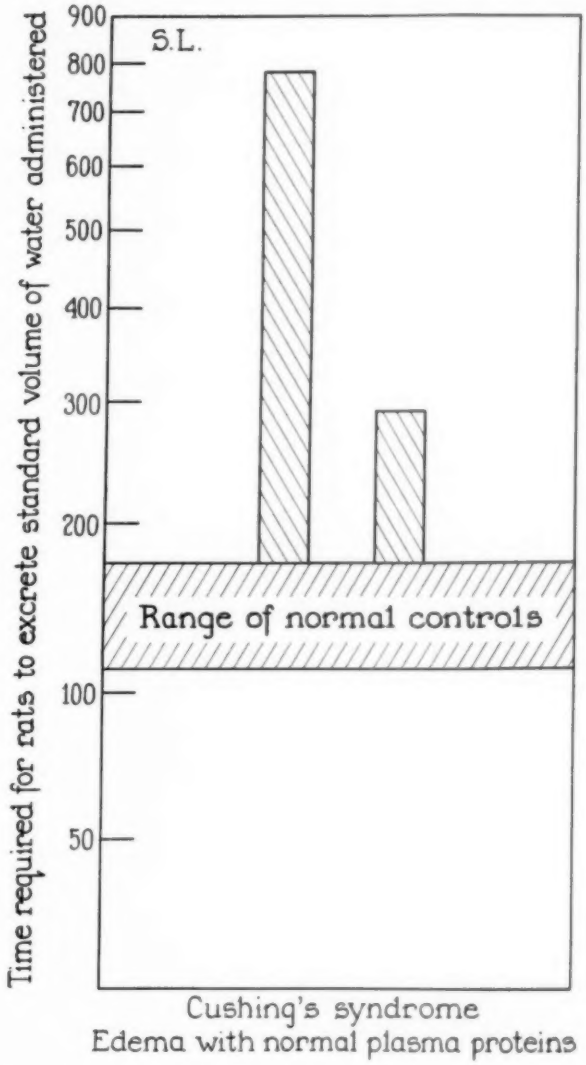

FIG. 7. Two assay series on a patient with Cushing's syndrome while edema was present. Both show marked increase in antidiuretic titer of the urine. The time is in minutes.

clearance. He found that dehydrated normal dogs excreted an antidiuretic substance in the urine and that the urine from these dogs contained a principle which would control the diabetes insipidus in the test animals. Urine

from dehydrated diabetes insipidus dogs had no effect under the same circumstances. Although this work does not give proof of the pituitary origin of the antidiuretic substance, it strongly supports the hypothesis that the pituitary plays an active rôle in the elaboration of the material. We did not carry out any studies on the origin or chemical nature of the material.

In view of the difficulties of interpreting the results obtained under controlled experimental conditions, it is obvious that we can offer no valid suggestions as to the cause of discrepancies which we have observed in some of

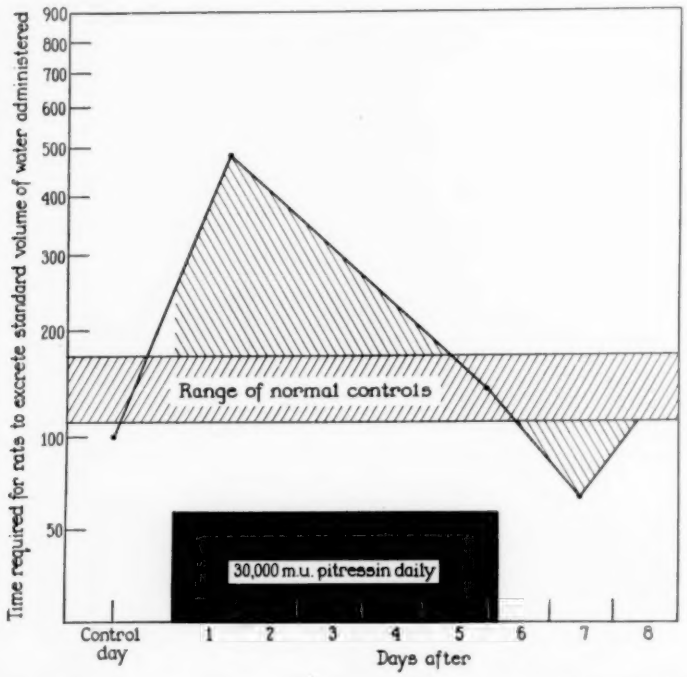

FIG. 8. The effect of continuous pitressin administration on the antidiuretic titer of urine obtained from a slightly edematous nephrotic patient. Note the marked increase in titer initially followed by a progressive fall, with the urine becoming actually diuretic on the fifth and subsequent days of pitressin administration. The time is in minutes.

our serial tests. On the other hand, the reproducibility of the results generally and the correlation with the presence or absence of edema in patients, and the uniform response which we were able to obtain after pitressin administration indicate that the results obtained by this method of assay cannot be artefacts. Doubt concerning the exact nature and derivation of the active principle does not impair its usefulness as a tool for the correlation of certain otherwise unrelated and unexplained facts of edema manifestations in patients.

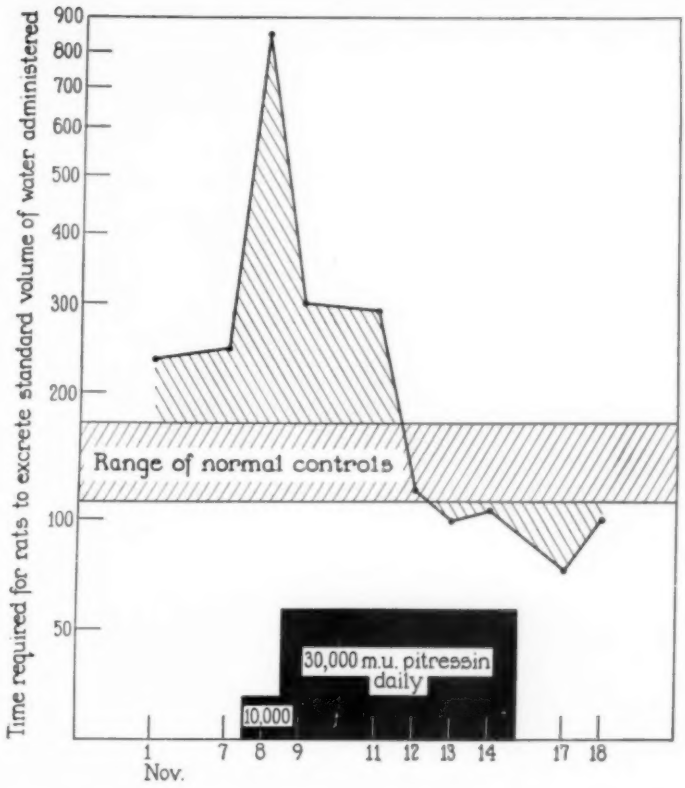

FIG. 9. The effect of continuous pitressin administration in the antidiuretic titer of urine obtained from a non-edematous nephrotic patient. The initial increase was followed by a fall to diuretic levels at the end of the period of pitressin administration. This response was quite uniform and could also be elicited in non-nephrotic subjects. The time is in minutes.

SUMMARY

Rat bioassays of the urines of patients with Bright's disease, premenstrual edema, Cushing's syndrome and diabetes insipidus, showed a correlation between the presence of clinical edema and the presence of an antidiuretic effect in concentrates of these urines.

This antidiuretic substance, demonstrable in the urines of three edematous patients with the nephrotic syndrome, was no longer demonstrable in the urine of two patients after all had become edema-free. The loss of edema occurred without rise in plasma proteins.

This antidiuretic substance was found in the urine of four patients with manifestations of acute nephritis whose edema could not be explained on a hypoproteinemic basis. In one patient studied after recovery, the antidiuretic substance was no longer present.

Four patients were given 30 units of pitressin parenterally daily for seven days. The antidiuretic effect of urine from these patients reached a maxi-

mum the first day of administration, thereafter decreased rapidly to the normal values. In three patients the urine became diuretic on the sixth day of continuous pitressin administration. The decrease in antidiuretic titer of the urines was paralleled by loss of edema initially resulting from pitressin administration.

Some limitations of the method were discussed.

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THE TREATMENT OF CHRONIC ULCERATIVE COLITIS WITH SULFANILAMIDE*

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During the past three years, sulfanilamide and its derivatives, such as neoprontosil and more recently sulfapyridine, have been used in the treatment of chronic ulcerative colitis. In this disease several types of organisms are commonly isolated from rectal scrapings and stools. When the same types of organisms are the cause of disease in other parts of the body, the use of the chemotherapeutic agents mentioned has proved valuable in certain instances. Therefore, it seems logical that patients having chronic ulcerative colitis, a serious and disabling disease, should be given the benefit of a trial on this form of therapy.

In this presentation, an attempt will be made to appraise the use of sulfanilamide in the treatment of a series of 33 cases. Neoprontosil alone was the chief chemotherapeutic agent in another group of five cases, and was used subsequent to sulfanilamide therapy in six additional cases. Therefore, a total of 44 cases comprises the basis of this report. Since sulfapyridine has been available only in recent months, an adequate period of time has not lapsed in which to appraise the use of this drug.

The type of colitis under discussion corresponds to the disease described by Bargen [1] and Buie [2] as "thrombo-ulcerative colitis." No cases of regional enteritis, so-called "right-sided" colitis, or the segmental forms are included. This report deals with diffuse, inflammatory, destructive, and hyperplastic processes which are seen by procto-sigmoidoscopic examinations to start in the rectum, and visualized by roentgen examination to extend in an upward direction in the colon.

Mode of Administration

When we first started using sulfanilamide three years ago, it was given orally in nontoxic cases and parenterally in severely toxic cases. An attempt was made to maintain a blood sulfanilamide level of between 8 and 10 mg. per 100 c.c. Toxic effects were observed quite commonly. We then tried giving sulfanilamide in smaller doses by retention enema (0.8 per cent solution). In the patients who made a satisfactory response, there were fewer toxic reactions, particularly less nausea, and it was thought that the results obtained by this method of administration were more satisfactory than when the drug was given by mouth. It was also thought that the direct contact of the drug with the mucous membrane might have an additional effect to that obtained by its presence in the systemic circulation.

* Read at the Cleveland meeting of the American College of Physicians, April 3, 1940.

In most of the cases where sulfanilamide was used, the drug was given by retention enema. A total of 45 grains in 24 hours has not been exceeded. This has resulted in maintaining a blood sulfanilamide level as high as from 5 to 7 mg. per 100 c.c. in certain instances. When possible, treatment is started in the hospital where the patient can be observed closely and daily blood counts can be made. If the drug is well tolerated, it is used for ten days or two weeks, then on alternate weeks in courses of two or three months with an interval of rest of one to three months after each course, depending upon the clinical course and the results of the progress examinations.

At the start of the treatment, one or two opium suppositories may be used daily. The sulfanilamide retention enemas are given four times daily but are not given close to meal time because of the gastrocolic reflex. A 45 grain powder of sulfanilamide is dissolved in a pint of warm distilled water, about one-fourth of this amount (125 c.c.) being again warmed to body temperature just before using as a retention enema. Men who later return to work may use from one-third to one-half of the pint at a time, depending on how many times daily it is convenient to take the enemas. As time goes on, the dosage of the drug or the frequency of its use is often reduced until it is used one week out of every three or four weeks. Because of the tendency of the disease to recur, we have found that it is important to use the drug in intermittent courses for some time, even after there is no evidence of activity.

When neoprontosil became available, we started using this derivative of sulfanilamide in alternate cases for a time, particularly in patients in whom close observation was not possible. The lower toxicity of neoprontosil in the treatment of chronic ulcerative colitis is established and it has been given by mouth only. At the start of treatment, 15 grains are given an hour before each meal, at bed-time, and at 3:00 a.m., a total of 75 grains per 24 hour period. The method is similar to that used by Brown, Herrell, and Bargen.[3] The initial period of use and its intermittent use thereafter are similar to those for sulfanilamide. If progress is favorable, the 3:00 a.m. dose is soon stopped so that 60 grains are received per 24 hour period. With continued improvement, the dosage is reduced further and the periods without the drug are lengthened.

In severely ill hospital patients who respond favorably to the use of either sulfanilamide or neoprontosil, our present impression is that results are obtained more quickly with sulfanilamide retention enemas than with the oral use of neoprontosil. Therefore, in certain instances, we have used sulfanilamide at the start of the treatment and have changed to neoprontosil before the patient is discharged from the hospital, and then continuing with the intermittent use of neoprontosil thereafter. We also have had this experience: The patient may have been started with neoprontosil and either developed an intolerance to the drug or the clinical course may not have been satisfactory, and he was advised to return to the hospital. Changing to sulfanilamide in this instance may result in a favorable course. At the

present time, neoprontosil is being used more frequently than sulfanilamide, particularly in the milder cases, because it is less toxic and oral administration is more convenient.

In recent months, the use of sulfapyridine by mouth in as small a dosage as 0.5 gram (7½ grains) four times daily, over a period of 10 days to two weeks at the start of treatment and then on alternate weeks in regular courses as mentioned above, has proved valuable. If a favorable response is noted, there is usually relief of symptoms soon after the drug is started and definite improvement in the proctoscopic findings may be noted within a period of a few weeks.

Soon after the report of McGinty, Lewis, and Holtzclaw [4] was published, stating that the administration of 50 mg. of nicotinic acid three times daily decreased the toxic symptoms experienced by patients receiving large amounts of sulfanilamide, we started using nicotinic acid in our patients at the times they were receiving sulfanilamide. In a few cases, studies were made on the urinary excretion of porphyrin-like substances before and after the administration of nicotinic acid but the results were contradictory. Vitamin deficiency states in the individual cases were probably a factor. However, since the administration of nicotinic acid has seemed to prevent toxic symptoms in certain instances, it is now routinely prescribed in cases of chronic ulcerative colitis when sulfanilamide is being used. Because of the lower toxicity of neoprontosil, nicotinic acid has not seemed to be indicated during the administration of this drug. Methylene blue has not been used in any of the cases in this review.

Classification of Cases

Previous reports [5, 6] have stated the difficulties in classifying cases, in appraising any single therapeutic measure in the treatment of chronic ulcerative colitis, or in comparing the results of one series of cases with another. Each case presents an individual problem. The variable severity of the disease and the fact that it is characterized by spontaneous remissions of symptoms and acute exacerbations must always be kept in mind. Progress proctoscopic examinations may reveal no change in the pathological process even though there has been a complete remission of symptoms. Jones [7] has mentioned that the rectal mucosa would seem to have immunized itself in these instances. Therefore, progress proctoscopic examinations are essential in judging the course of the disease.

In grouping cases, the use of Kiefer's classification of chronic ulcerative colitis [8] has proved helpful (table 1).

Table I

Kiefer's Classification of Chronic Ulcerative Colitis

Group I.	Non-toxic, afebrile, non-sclerotic
Group II.	Non-toxic, afebrile, sclerotic
Group III.	Toxic

Although Kiefer has not observed a close correlation between the clinical severity and the amount of colon involvement, in our experience the cases which have been placed in Group I are usually early cases, and in most instances, the morbid process, as shown by roentgen examination, is limited to the rectum and sigmoid colon. In our present series of cases, we have not seen a case where evidence of toxicity is lacking in Kiefer's Group II. Therefore, in this review, the cases will be placed into either the non-toxic, afebrile group, or the toxic group. The extent of the process as revealed by roentgen examination and other criteria used by Brown, Herrell, and Bargen [3] will be quoted.

Table 2 gives a report of the use of sulfanilamide in a nontoxic, afebrile group of cases.

TABLE II

Afebrile Cases, Sulfanilamide

Case	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	10	4–10	R.S.	Quiescent	35	1
2	6	15+	R.S.	Norm. muc.	30	1
3	4	6–9	R.S.	Quiescent	29	1
4	1	2–4	R.S.		29	3
5	1	15+	R.S.		25	3
6	2	2–4	R.S.	Improved	24	3
7	13	6–8	R.S.		23	1
8	2½	3–6	R.S.	Quiescent	18	1
9	6	4–6	R.S.	Norm. muc.	17	1
10	5	4–16	R.S.	Norm. muc.	16	1
11	3	2–4	R.S.		16	1
12	1	3–6	R.S.	Quiescent	12	2
13	6	15+	S.F.	Quiescent	7	?*

Key: R.S.—rectum and sigmoid
S.F.—splenic flexure.

1—complete and continuous remission
2—mild recurrence with recovery
3—unsatisfactory response.

* See case report.

In the tables no mention is made relative to age or sex incidence. Although this disease may occur at any age, it develops mostly in young adults between the ages of 20 and 40 years. The sex incidence is about equal. The heading, "duration of disease in years," includes the time of onset of the disease until the time that sulfanilamide therapy was started. The disease may have existed intermittently during the times stated. The severity of the disease in each individual case cannot be described accurately. However, the duration of the disease, the number of stools passed daily, and the extent of involvement at the time of the initial examination give some idea of the severity and the degree to which the patient was incapacitated by this disease.

In each case, smears and cultures were made from rectal scrapings and from stools as soon as they were passed. There was no evidence of parasitic infection. The initial proctoscopic examination in all cases revealed a diffuse inflammatory process, as defined above, and in every case the disease was active at the time sulfanilamide therapy was started. The findings on progress proctoscopic examinations by us and the duration of follow-up studies are quoted. In the instances where no progress proctoscopic findings are given, these examinations may have been made elsewhere, but not in the Cleveland Clinic. The term "quiescent" means that there was no evidence of activity at the time of the proctoscopic examination. Some scarring of the mucosa or contracture of the lumen may have been present, but no bleeding was observed on swabbing. Since it is possible for a patient with this disease to have a remission for three years, the word "cure" is not mentioned.

Afebrile, Non-Toxic Cases

In an analysis of table 2, it will be noted that in eight, or 60 per cent of the 13 cases, the patients have had a complete and continuous remission, in several instances over a period of more than two years. In 10, or 76 per cent, sulfanilamide was considered valuable, and was the only special form of treatment used. Case 13 was a man who was severely incapacitated by this disease at the time sulfanilamide therapy was started, 32 months ago. We previously had used several types of treatment, including autogenous vaccines, without obtaining desirable lasting effects. He made a favorable response to sulfanilamide therapy and returned to work within one month. Several progress proctoscopic examinations over a period of the next seven months revealed a quiescent stage of the disease. He has not been observed since that time.

It will be noted that roentgen examinations in this group of non-toxic cases revealed no evidence of extension of the disease above the sigmoid colon, with the exception of one case where it had extended to the splenic flexure.

Toxic, Febrile Cases

Table 3 shows that in 10 cases receiving medical management to date, which are placed in Kiefer's Group III (febrile-toxic), only four or 40 per cent have obtained a complete and continuous remission. In case 10 the referring physician recently stated that the patient's general condition is much improved but there has been incomplete relief of symptoms. This patient originally had had a high fever and had been bed ridden. She is working daily now and is taking sulfanilamide one week in every four weeks.

Table 3 does not include an additional group of five severely toxic cases in which ileostomy or other surgical procedures were used after sulfanilamide therapy failed. In two of these cases, multiple perforations were found at

TABLE III

Toxic, Febrile Cases, Sulfanilamide

Case	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	5	10–15	E.C.		37	3
2	2/3	15+	H.F.	Quiescent	30	1
3	14	15+	H.F.	Improved	30	1
4	10	9–10	S.F.	Quiescent	28	3
5	3	3–10	S.F.	No change	26	3
6	1½	15+	E.C.	Quiescent (polyps)	24	3
7	3	3–4	R.S.	Normal (contrac.)	23	1
8	11	15+	R.S.	Imp. then recur.	20	3
9	3	9	E.C.		14	1
10	2/3	12–15	R.S.		9	?

Key: R.S.—rectum and sigmoid
S.F.—splenic flexure
H.F.—hepatic flexure
E.C.—entire colon.

1—complete and continuous remission
3—unsatisfactory response.

the time of operation and it was believed that this situation existed prior to the institution of sulfanilamide therapy. Death occurred in both instances.

Death occurred in two other severely toxic cases in which sulfanilamide therapy had been used. One patient who was 76 years of age died after operation for prostatic obstruction. In the other case, sulfanilamide was used for only six days.

Sulfanilamide therapy might have been expected to have a beneficial result in three of the cases in which surgery proved necessary as a life-saving procedure. In combining these three cases with the ten toxic cases receiving medical management, it is apparent that only 30 per cent of this group have had a remission which may be attributable to the use of sulfanilamide.

In tables 4 and 5 is a group of patients in which sulfanilamide and neoprontosil, or neoprontosil alone were given, each at different times. Because of the relatively small series of cases in this group, the non-toxic and toxic cases are grouped together.

In an analysis of tables 4 and 5, eleven non-toxic and toxic cases received sulfanilamide and neoprontosil, each at different times, or neoprontosil alone. Three cases have had a continuous remission, with proctoscopic examinations revealing normal findings; six cases have had mild recurrences with recovery, and in only two cases has this form of therapy been discarded to date. The features which need emphasis in this group are the small number of cases and the relatively short period of follow-up studies. However, consideration is given this group because it shows trends and possibilities in the treatment of this serious disease.

Clinicians who are particularly interested in treating this disease know that any therapeutic procedure which has shown promise of relieving the

patient's disability should be given an adequate trial. In several cases observed in recent months, the use of relatively small oral doses of sulfapyridine has resulted in a favorable response but an adequate period of time has not lapsed in which to appraise the use of this drug.

TABLE IV

Sulfanilamide and Neoprontosil (Oral)

Case	Group	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	S.T.	2½	10–14	E.C.		35	2
2	S.T.	½	6	E.C.	Quiescent	26	2
3	S.T.	¼	Invol.	E.C.	Quiescent	15	2
4	A.	3	12	R.S.	Norm. muc.	10	1
5	M.T.	¼	6–12	R.S.	Recur.	7	3
6	S.T.	1	15+	E.C.	Improved	7	2

Key: A.—afebrile
S.T.—severely toxic
M.T.—mildly toxic
R.S.—rectum and sigmoid
E.C.—entire colon.

1—complete and continuous remission
2—mild recurrence with recovery
3—unsatisfactory response.

TABLE V

Neoprontosil (Oral)

Case	Group	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	A.	27	15+	E.C.	Quiescent (polyp)	11	2
2	A.	2	3–4	R.S.	Norm. recur.	11	2
3	M.T.	7	15+	S.F.	Norm. muc.	7	1
4	M.T.	1	7	S.F.	Norm. muc.	7	1
5	M.T.	3	8–10	E.C.	Improved	8	3

Key: A.—afebrile
M.T.—mildly toxic
S.T.—severely toxic
R.S.—rectum and sigmoid
S.F.—splenic flexure
E.C.—entire colon.

1—complete and continuous remission
2—mild recurrence with recovery
3—unsatisfactory response.

OTHER FORMS OF TREATMENT

It is difficult to evaluate any single therapeutic measure in this disease because the plan of management has included well-known factors pertaining to diet, rest, vitamin and mineral deficiencies, and the administration of blood transfusions and parenteral fluids in severely toxic cases.[6] Mackie,[9] Willard, Pessel, Hundley and Bockus[10] and many others have emphasized the need for a multiple approach in the treatment of chronic ulcerative colitis. There-

fore, sulfanilamide and/or its derivatives should be considered as an *adjunct* to the usual therapy and certainly not as a specific remedy. However, in many of the cases cited in this review, this adjunct was not used until after the usual forms of therapy had proved ineffective. No patient who has made a favorable response to sulfanilamide therapy has received sera or vaccine since this form of chemotherapy was instituted. In our experience, when a patient makes a favorable response to this form of therapy, this occurs more quickly than has been observed with other forms of medical management. A decision relative to its effectiveness is usually made within seven to fourteen days.

The effective treatment of chronic ulcerative colitis depends upon the various features presented by the individual case, such as evidence of toxicity, the degrees of deformity or complications in the colon, the duration of the disease, the types of treatment that have already proved ineffective, and the variable severity of the disease in general. The patient may present evidence of irreparable damage at the time of the initial examination. Education of the patient and his family as to the seriousness of the disease, and the usual life history of an individual having this disease is of great importance, at the start of treatment. Certain complications constitute definite indications for surgery, such as stricture, polyposis, neoplasm, and perirectal abscess. In pointing out other indications for surgery, Jones [7] has found that with each acute exacerbation of the disease it tends to extend to more proximal segments of the colon. In all toxic cases, at least, we believe the surgeon should be in constant attendance with the internist. It is hoped that the surgical indications will become as well defined in this disease in the near future as they are now established in the case of peptic ulcer.

The aim of medical management should be not only to produce a remission of the disease but also to prevent the ultimate need for ileostomy, if not colectomy. The decreasing use of surgical procedures in a large series of cases reported by Bargen [1] and Buie [2] is significant. However, if medical management does not prevent acute exacerbations, and progress roentgen examinations show that the disease is extending orad in the colon, how long should we wait before instituting surgical procedures? A colostomy (division of the bowel and its mesentery) in the mid-transverse colon results in less disability to the patient than ileostomy. When a patient's progress is not satisfactory on medical management, should this procedure be used earlier in the course of the disease than is customary? If this were done in these instances, possibly the continued use of the newer developments in medical management (as they appear) would permit the gastrointestinal lumen to be reëstablished later.

Comment

Brown, Herrell, and Bargen [3] presented their appraisal of the use of neoprontosil in the treatment of chronic ulcerative colitis before this college one year ago. Our experiences in a smaller series of cases coincide with their

observations. Since sulfanilamide was introduced prior to neoprontosil and the duration of a remission is significant in this disease, our experiences with these forms of chemotherapy were considered worthy of record.

Chronic ulcerative colitis is now recognized earlier in the course of the disease, probably because of the more frequent use of stool, proctoscopic, and roentgen examinations of the colon in any patient who has dysfunction of the colon. We believe our present study indicates that the use of sulfanilamide and/or its derivatives is of greatest significance when used early in the course of the disease.

After an experience of three years, we now routinely give each patient the benefit of a trial on this form of therapy. If the drug is well tolerated, its continuance or discontinuance is based on the response of the individual patient within a period of seven to fourteen days.

Summary and Conclusions

An appraisal is made of the use of sulfanilamide and/or neoprontosil in the treatment of chronic ulcerative colitis during the past three years.

Careful observation of the patient and repeated blood counts must be made during the administration of these chemotherapeutic agents. Three of the patients in this series made a satisfactory initial response to sulfanilamide therapy but later developed an intolerance to the drug. The immediate discontinuance of sulfanilamide resulted in the clearance of these reactions and no patient in this study has had serious sequelae because of this form of chemotherapy.

Death occurred in four instances subsequent to the use of sulfanilamide therapy. All four patients had extensive, if not irreparable damage to the entire colon and were severely toxic at the time of admittance to the clinic. Multiple perforations of the colon were found at the time of operation in two patients, the third patient was 76 years of age and died after an operation for prostatic obstruction, and sulfanilamide was used only six days in the fourth patient.

Ileostomy has been performed on three other severely toxic patients after the failure of sulfanilamide therapy. In combining these three cases with 10 *toxic* cases receiving medical management, a remission which may be attributable to the use of sulfanilamide occurred in only four of this group, or 30 per cent.

In a group of 13 *non-toxic* cases, a complete and continuous remission has occurred in eight or 60 per cent, in several instances over a period of more than two years. In ten or 76 per cent, sulfanilamide was considered valuable and was the only special form of treatment used.

In a general appraisal of the use of sulfanilamide in 26 cases, combining both *non-toxic* and *toxic* cases, in which the use of this drug might have been expected to prove significant, favorable responses were obtained in 15 cases, or 57 per cent.

We therefore believe that sulfanilamide has a place in the treatment of chronic ulcerative colitis. It should be considered an *adjunct* to the usual forms of treatment and not as a specific remedy. It has proved of greatest value in the early non-toxic stage of the disease.

Experiences with neoprontosil and sulfapyridine are mentioned but the small number of cases and the relatively short period of observation since treatment was started permit only initial impressions.

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CONCERNING THE CORRELATION OF THE PATHOLOGY AND SYMPTOMS OF CORONARY ARTERY DISEASE *

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The fact that it is often difficult or perhaps impossible to correlate the pathology and symptoms of coronary artery disease has led to a great deal of discussion and numerous explanations have been proposed. Developments during recent years, however, have contributed much to better understanding of the problem.

Certain aspects of the pathology have a particular bearing on the diverse symptoms. In the first place, it is generally known that the heart may be normal in size in the presence of extensive sclerosis of the coronary arteries. Thus, in 113 cases analyzed by Nathanson,[1] selected because they presented advanced stage of the disease with marked narrowing or obstruction of one or more of the larger arteries, 45 (40 per cent) weighed 400 grams or less. Furthermore, in 12 of the 24 with occlusion of one of the main branches the weight of the heart did not exceed 400 grams. In a series of cases reported by Applebaum and Nicholson [2] the weight of the heart in 25 of the 94 was within the range of normal set at 400 grams. Palmer [3] studied the size of the heart roentgenologically in 200 patients who had survived coronary thrombosis by at least three months. About one-third of the series failed to show or to develop definite cardiac enlargement although observed over a period averaging more than three years following the coronary accident and despite the fact that several had subsequent attacks.

Jores [4] and others have pointed out that the arteriosclerotic process involves mainly the larger and medium sized vessels and that the arterioles are rarely concerned. Saphir, Priest, Hamburger, and Katz [5] from the study of 34 hearts with advanced disease of the coronary arteries found no relation between the gross lesions in the larger branches and the histological changes in the smaller vessels (arterioles). They stated that often the latter showed no significant alterations in the presence of pronounced arteriosclerosis of the larger arteries; that intimal thickening of the arterioles was disclosed in only a few sections from the myocardium and that obliterating endarteritis was not observed in a single instance. Moreover, in the arteriolar sclerosis of hypertension the arterioles are usually implicated to a minor extent as compared to the degree of involvement found in other organs.[6] This is of great significance, for the smaller branches serve an important function in the development of collateral circulation.

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Disease of the coronary arteries frequently progresses to an advanced stage before symptoms appear. While the condition is generally more extensive in one vessel, particularly the anterior descending branch of the left coronary artery, the other main branches are usually involved to varying extent. This feature was especially emphasized in the report by Saphir and his co-workers. Both coronary arteries were involved in each of the 34 hearts examined. In those with myocardial infarct at least two branches supplying this particular area were involved. The infarction was usually located in the area supplied by the occluded artery. There were instances, however, in which a recent thrombus was found in one vessel and the resulting infarct was located in an area supplied by a previously occluded adjacent artery. These observers also noted the presence of infarct in four instances in absence of occlusion. It was observed, however, that the lumen of these vessels was greatly reduced. Similar results have been recorded by Schlesinger [7] and still more recently by Blumgart, Schlesinger, and Davis.[8] Schlesinger cited one instance in which there was an adequate injection throughout the heart even though both main branches of the left coronary artery and the main stem and the larger branch of the right coronary were occluded. The more recent obstruction concerned the circumflex branch of the left coronary artery but an infarct did not result. Moreover, despite the multiple occlusions of the main branches of the coronary arteries there was very little fibrosis of the myocardium. In this connection it is well to bear in mind that the orifices of the coronary arteries may be obstructed by syphilitic process without the production of infarction, such as in the two cases reported by Leary and Wearn.[9] The hearts weighed 328 and 285 grams respectively and there were no significant histological changes.

There is also great diversity in the extent of the fibrosis of the myocardium, even in the presence of extensive disease of the coronary arteries. Oberhelman and Le Count [10] indicate that there may be no gross or microscopic changes in the cardiac muscle following the closure of either the right or left coronary artery and cite the observations of Galli and Merkel. In the series of 113 cases studied by Nathanson the fibrosis varied from slight to extensive degree. Schlesinger and others have also commented on the variability of this aspect of the pathology.

It is apparent that the heart may withstand repeated major insults to the coronary circulation without gross and perhaps microscopic changes in the myocardium. This can be explained only on the basis of the development of collateral or accessory circulation. The experimental ligation of one of the main branches of the coronary arteries, in my experience, has always produced an area of infarction.[11] It is quite probable that under similar circumstances the same would obtain in man. With normal coronary arteries, therefore, it would seem that if the blood supply to a large area of the myocardium is suddenly interrupted it is not possible for this to be completely restored by an adjacent vessel. The fact that there is rather striking

variation in the size of the resulting lesion when the same vessel is ligated at corresponding levels would indicate at least that in certain instances there is considerable collateral circulation. Anastomosis between adjacent normal vessels no doubt varies in extent, probably effective for the most part through the smaller branches, or perhaps may exist only in a potential state until there is need for it. Wiggers [12] concluded that the communication between normal vessels is extremely small but further states that this does not preclude the enlargement of minute potential channels nor the development of new ones when a main branch is slowly occluded. The investigation by Blum, Schauer, and Calef,[13] however, demonstrated that effective collateral circulation may develop in a relatively short time. These observers studied the effects of gradual occlusion of the anterior descending branch of the left coronary artery in 14 dogs over periods averaging five weeks in duration. In ten of these animals there was no gross evidence of an infarct, and moreover in four there were no histological changes in the myocardium.

It is well known that there is commonly free communication between vessels in which one has been gradually occluded. The need for this is obvious and has been repeatedly emphasized. This question has more recently been investigated by Schlesinger using an improved method consisting of a combination of multicolored radiopaque injection material and complete dissection. In a group of 35 hearts taken from patients over 55 years of age extensive collateral circulation was disclosed in only those instances in which there was occlusion of the coronary arteries. It is of interest to note, however, that anastomosis was demonstrated in five hearts in which the coronary arteries presented only few scattered atheromatous plaques. Wearn and his associates [14] and others have shown that under adverse circumstances the thebesian veins may contribute to the blood supply of the myocardium. Finally, Beck and Tichy [15] and Robertson [16] have demonstrated the importance of extra cardiac circulation. In the investigation by Robertson the coronary sinus, the main veins, and the coronary arteries were successively ligated, and finally in certain instances the pericardial adhesions were later separated. In the typical protocol cited, the first procedure was carried out February 20 and the final one, the sixth, August 18. In the last operation the pericardium was stripped from the myocardium. The dog died in October from cardiac failure. These operations resulted in the development of extensive communications between the vessels of the heart and those of adjacent structures which were regarded as being mainly responsible for the maintenance of the cardiac circulation.

The initial symptom in coronary artery disease is usually either shortness of breath on exertion, sudden onset of dyspnea, angina of effort, or severe anginal pain from coronary thrombosis. In the cases in which the onset is that of the gradual development of shortness of breath the disease of the coronary arteries is often supplemented by other factors such as hypertension, chronic valvular heart disease, etc., which increase the demands on the

heart. The sudden onset of intense dyspnea (acute left ventricular failure) as the first intimation of cardiac disability is usually due to coronary thrombosis. The occurrence of coronary thrombosis without pain is far more common than generally appreciated. In 53 autopsied cases analyzed by Davis[17] there were 21 that did not give history of pain. Others have estimated that 30 to 50 per cent do not have significant distress.[18, 19]

The greatest discussion has been concerned with the explanation of the pain of angina pectoris. Of the numerous theories that have been proposed the concept that the pain results from inadequate blood supply to the myocardium has had the largest following. The identification of the syndrome of coronary thrombosis and the fact that the pain in this condition is indistinguishable from that of angina pectoris except perhaps from the standpoint of intensity again focused attention on the coronary arteries. Subsequent investigations have fully convinced most of those interested in the field that a deficiency in the blood supply to cardiac muscle is the basic factor in the production of the pain in the vast majority of the cases. There are two features in particular, however, that are difficult to explain on this hypothesis. In the first place there are occasional instances such as reported by Leary in which there are no significant changes in the coronary arteries. Furthermore, as emphasized by Saphir and his co-workers it is not possible to determine at necropsy which patients have had pain. Thus, in 18 of their 34 cases there was history of angina pectoris and in a number of these the heart presented coronary thrombosis, arteriosclerotic occlusion, and myocardial infarction. There were others, however, with the same pathological changes that apparently did not experience pain. Furthermore, equally extensive lesions were disclosed in cases in which there was no history of cardiac disability. Blumgart, Schlesinger, and Davis [8] have recently reported an extensive investigation concerned primarily with the relation of the pathologic process to the clinical manifestations of coronary artery disease. Of the 30 cases studied there were 12 in which angina pectoris was the primary condition. Ten of these had old complete occlusion of at least two main coronary arteries. In the remaining two one of the main coronary arteries was closed and the other two were partially obstructed. There were also five cases in which the angina was a later development. In one it was preceded by congestive failure and the subsequent occurrence of coronary thrombosis. Three had advanced rheumatic valvular disease and one cor pulmonale. In one of the cases with valvular heart, that of a young man 26 years of age, there was no demonstrable disease of the coronary arteries. There was a history of repeated recurrence of severe rheumatic infection and the predominating lesion was that of high grade aortic insufficiency, the blood pressure being 200 systolic and 20 diastolic. It was concluded that the anatomical alterations in every case were consistent with the theory that angina pectoris is the result of the paroxysmal occurrence of relative myocardial ischemia. However, the presence or absence of pathological changes

in the coronary arteries was not always the sole factor which determined the presence or absence of angina pectoris.

Angina pectoris in the absence of significant coronary artery disease is undoubtedly rare and is generally associated with factors which impose excessive demands on the heart. Cases of this type have directed attention to other possibilities and of these increased vasomotor tone or spasm has received increasing support from investigations of recent years. The association of indigestion with angina pectoris suggesting reflex connection between the stomach, gall bladder, esophagus, and the heart is a common observation. Von Bergmann [20] reports that the inflation of a balloon in the stomach of the dog produces vasoconstriction of the coronary arteries which is abolished by atropin or section of the vagus. These results have since been confirmed by Gilbert, Fenn, and Le Roy.[21] Morrison and Swalm [22] tried out the effects of distending a balloon introduced into the esophagus or stomach of two patients with angina pectoris. In both the pain was induced and in one there was a pronounced reduction in the cardiac rate. The distress promptly disappeared following the release of the pressure within the balloon. That vasomotor changes may play a rôle in the production of pain is further indicated by the investigation of Hall, Ettinger, Banting, and Manning [23] in which it was shown that it was possible to produce changes in the myocardium by prolonged or repeated vagal stimulation.

There are still wide gaps in our knowledge regarding the explanation of anginal pain. Of the various possibilities, however, it is obvious that the production of pain is dependent on the presence of receptive sensory nerve endings. Katz, Mayne, and Weinstein [24] have demonstrated in the dog that if the nerves accompanying a coronary artery are blocked the obstruction of the vessel apparently does not cause pain. Furthermore, stimulation of the nerves seems to produce the same reaction as the ligation of the vessel and the surrounding structures. Thus, the receptive state of the sensory nerve endings may account for absence or presence of pain. Finally, it is generally known that there is great variation in the individual response to pain. This has been emphasized by Libman [25] and referred to in different connections by numerous observers. Stewart Roberts [26] has stressed this factor in angina pectoris and believes that it is largely responsible for the low incidence of the disorder in negroes.

Conclusions

In coronary artery disease the changes in the arteries are the only constant feature. The response of the heart in any particular instance is no doubt influenced by many factors but the ability to maintain an adequate circulation to the myocardium through the development of collateral circulation is perhaps the most important. Clinical and experimental studies have demonstrated that this is more effectively accomplished if there is a gradual occlusion of the vessels. In the normal subject the communications between

adjacent vessels are limited and in most instances by means of the smaller vessels. Therefore, the abrupt closure of one of the main vessels early in the course of the disease usually results in a large area of infarction. If, on the other hand, the obstructive process develops slowly and is not terminated too soon by a thrombus there may be very little or perhaps no significant degeneration of the myocardium. Thus, the rate of the formation of the obstruction determines in a large measure the extent of the collateral circulation, the histological changes in the myocardium, the efficiency of the heart, and quite probably the character of the clinical expression.

Of the various symptoms pain is the most difficult to explain. Most workers in this field believe that insufficiency in the coronary circulation is the basic factor. Two features in particular, however, are difficult to explain on this hypothesis. In the first place, there is an occasional case in which there is no demonstrable disease of the coronary arteries or if present is regarded as being insignificant. Moreover, many with advanced disease of the coronary arteries never have angina pectoris. In the former the angina is usually associated with conditions which impose excessive demands on the heart. There is also the possibility that increased vasomotor tone or spasm may be a factor. Finally, in the cases of extensive disease of the coronary arteries the receptive state of the sensory nerve endings, or perhaps the nervous mechanism in general, may determine the presence or absence of pain.

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MALARIAL COMA *

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Coma as the presenting manifestation of disease is a challenge to the diagnostic and therapeutic skill of the physician. This is true not only because coma is often of serious omen but also because an informant is frequently not present and little or nothing can be learned of the history of the illness. The physician must depend in many instances, therefore, on objective findings alone.

The records of all patients admitted in coma to the John Gaston Hospital during the past five years have been reviewed. Of 73,782 admissions, 1,021 were comatose, an incidence of 1.4 per cent.

Many of the articles dealing with coma have failed to mention malaria. One reason for this is that most of the contributions to the subject have come from writers in non-malarial districts. Those of us who practice in localities where malaria is common can attest that it is an important factor in the production of coma. In our series it stood seventh, accounting for 4.7 per cent of all comatose admissions.

Table I

Analysis of 1021 Cases Admitted in Coma

Diagnosis	Number	Per Cent	Diagnosis	Number	Per Cent
Cerebral vascular accident	219	21.4	Cerebral tumor	4	0.4
Head injury	187	18.3	Cerebral arteriosclerosis	4	0.4
Meningitis	114	11.2	Convulsions, unclassified	3	0.3
Uremia	80	7.8	Spasmophilia	3	0.3
Chemical poisoning	59	5.7	Cirrhosis of liver	2	0.2
Lobar pneumonia	56	5.5	Hemorrhage	2	0.2
Malaria	48	4.7	Acute yellow atrophy	2	0.2
Alcoholism	43	4.2	Cerebral abscess	1	0.1
Syphilis of C. N. S.	43	4.2	Pernicious anemia	1	0.1
Toxemia of pregnancy	39	3.8	Electrical shock	1	0.1
Diabetes mellitus	32	3.1	Exposure to cold	1	0.1
Hypertensive encephalopathy	31	3.0	Stokes Adams syndrome	1	0.1
Epilepsy	13	1.2	Acidosis (non-diabetic)	1	0.1
Encephalitis	12	1.2	Hyperinsulinism	1	0.1
Typhoid fever	6	0.6	Diphtheria	1	0.1
Exposure to heat	6	0.6	Ascaris lumbricoides infestation	1	0.1
Hysteria	6	0.6			

Reference to table 1 will show that in our series the diseases responsible for coma on admission more frequently than malaria were cerebral vascular accident, head injuries, meningitis, uremia, chemical poisoning and lobar

* Read at the Cleveland meeting of the American College of Physicians April 3, 1940.

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pneumonia. Alcoholism was a less frequent cause of coma than malaria. It ranked eighth in our series, being responsible for 43 cases, or 4.2 per cent. This is a rather sharp contrast to Solomon's [1] observation in his analysis of the causes of coma on admission to the Boston City Hospital. In his series, 59 per cent were due to alcoholism. This, however, should not be taken to indicate that Memphis is a more temperate city than Boston. In Memphis a special provision is made for the care of the victims of alcoholic intoxication and they are usually not admitted to the John Gaston Hospital.

It is usually easy to explain the fluctuation in the prevalence of malaria, as it is related to the amount of rainfall and other factors influencing the propagation of mosquitoes. The incidence of malarial coma, as well as that of malaria itself, varies considerably from year to year as is shown in table 2. We are not able to explain the fact that in 1935 coma was present in 8.5 per cent of all malarial patients, while in 1939 the incidence was only 0.9 per cent.

TABLE II

Incidence of Malarial Coma

Year	Total	Coma	Per Cent
1935	327	27	8.5
1936	142	6	4.2
1937	165	7	4.2
1938	164	6	3.6
1939	220	2	0.9

It will be seen from the accompanying graph, figure 1, that there is a very decided seasonal incidence of malarial coma. Most of our cases were admitted in August and October. It will be observed further that not a single case occurred during the months from February to June. This high incidence of coma during the fall is accounted for by the prevalence of estivo-autumnal malaria during that season.

While it is well known that estivo-autumnal malaria generally occurs in the fall and tertian infections are more common in the spring and early summer, the reason for this variation has not been definitely shown. The hypothesis that tertian merozoites prefer reticulocytes to older red blood cells and that reticulocytes are more numerous in the blood in the spring may explain the frequency of that type of infection during that season. No reason is apparent, however, for the seasonal predilection of estivo-autumnal malaria.

A rather unusual feature of our series is that three of our 48 cases were tertian infections. Two other patients were infected with both estivo-autumnal and tertian parasites. The following is a brief résumé of the three tertian cases:

Case 1. A negro male, about 40 years of age, was admitted in coma. No informant was present and a history was not obtainable. The admission temperature was 95 degrees Fahrenheit and the patient was in shock. Tertian parasites were present in the blood smear. The patient did not respond to treatment and died 17

hours after admission. He did not regain consciousness. A necropsy could not be obtained.

Case 2. A white man, 71 years old, was comatose on admission. The initial temperature was 99.8 degrees Fahrenheit. Tertian parasites were found in the blood smear and in a thick drop preparation. Consciousness returned about 24 hours after admission, the temperature became normal two days later and he was discharged improved at the end of five days.

Case 3. A white male, 32 years of age, was admitted in coma. He had been ill for eight days, but the duration of coma was not known. His temperature was 105 degrees Fahrenheit. Tertian parasites were found in the blood smear. Coma continued for two days, the temperature became normal at the end of three days and he was discharged improved at the end of six days.

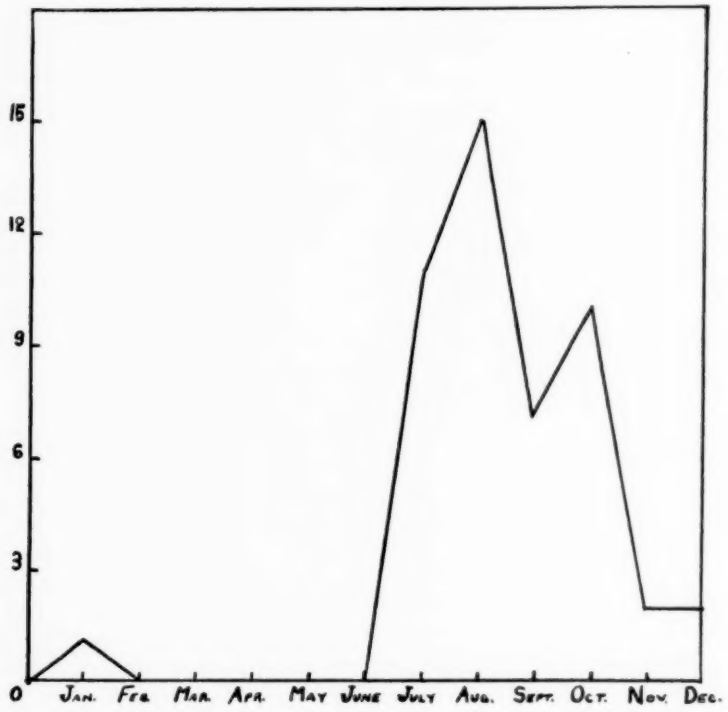

FIG. 1. Seasonal distribution of malarial coma.

Coma developed in these cases of tertian infection, presumably, as a result of toxemia. While tertian malaria is generally considered a benign disease, it is well known that it may occasionally become very malignant. It is conceivable, therefore, that coma may occur in tertian malaria in the same way it occurs in lobar pneumonia, typhoid fever and other infectious diseases.

It is possible that toxemia is also a factor in coma resulting from estivo-autumnal infections. Hegner [2] attributes the greater toxicity of estivo-autumnal malaria to a lack of preference of that type of parasite for reticulocytes. This obviously predisposes to a more prolific invasion of red cells.

Many tertian merozoites are killed by antibodies in the plasma or are engulfed by phagocytes while seeking a preferred reticulocyte to enter. Hingst [3] demonstrated by photomicrographs that the estivo-autumnal parasite is capable of undergoing direct as well as multiple division and can produce many more merozoites at the time of sporulation than any other type.

However, malarial coma is usually caused by the plugging of large numbers of cerebral capillaries by parasitized red cells. The reason estivo-autumnal plasmodia are more apt than other varieties to obstruct capillaries is ingeniously explained by Bass.[4] He has demonstrated that the estivo-autumnal parasite is firm in consistency and lacks ameboid movement so that it cannot change its shape to conform to the lumen of the vessels.

Coma in malaria is obviously an evidence of neglect. Malaria is very amenable to treatment and no patient adequately and fairly promptly treated should become comatose. The average duration of illness in our series when a history could be obtained was 12 days. Naturally, the disease should and could have been brought under control long before this period.

The geographical distribution of malarial infection is well known. With our modern means of transportation, however, diseases are no longer limited to certain areas. It is quite easy for an individual infected with malaria in the South to reach a distant portion of the country during the period of incubation. It is conceivable that such an individual would be more likely to become comatose under these circumstances than if he remained in the South, because physicians in non-malarial districts are not " malaria conscious " and would be more likely to overlook the cause of disease. It is the opinion of the authors that malarial coma may be more widespread than has previously been realized.

The diagnosis of malarial coma is not difficult. Fever is usually present, though not always. Some patients are in shock and have a sub-normal temperature. Thirty-nine of our 48 patients had an elevated temperature. The seasonal incidence will naturally make one think more seriously of malaria as a possible cause of coma in the late summer and fall. A history, if available, of probable exposure to malaria infested mosquitoes or of recent illness with chills and fever is of value. A lemon colored tint of the skin is often seen. Occasionally the skin will present a " muddy " discoloration which, according to Bass,[5] is due to phagocytosis of malaria pigment by the endothelial cells of the capillaries. The liver and spleen are enlarged in malarial infections. These organs may usually be palpated in malarial coma. Evidences of dehydration are common. Examination of the blood usually reveals a reduction in number of red blood cells and in percentage of hemoglobin. The total number of leukocytes is generally around normal in malarial infections, but the percentage of mononuclear cells is increased. In coma, however, a leukocytosis may occasionally occur. It was present in five of our cases and in these the white cells ranged from 10,450 to 30,000. Obviously, the diagnosis is definitely made by finding the parasites in the blood smear or thick drop preparation. It is usually not difficult to find the

organisms in malarial coma, because they are quite numerous by the time coma develops.

That coma is a serious complication of malaria is indicated in our series by the fact that 19 of our 48 patients died, a mortality rate of 40 per cent. The average duration of coma prior to admission in our cases in which a history could be obtained was 17 hours. Several of our fatal cases might have been saved had they received adequate treatment in an earlier stage of their coma. Coma does not develop in malaria, however, until the infection has become overwhelming. It should always be considered, therefore, with gravity.

In the treatment of malarial coma one must bear in mind that one is dealing with an emergency. A drug which is rapidly effective should be selected and it should be administered in a manner that will insure prompt action. Quinine dihydrochloride or any other water-soluble quinine compound, given intravenously, meets these requirements. The maximal initial dose of ten grains should be given to the average sized adult. Clinicians differ as to the desirable dilution for intravenous administration. Bass[5] recommends that it be given in 20 c.c. of normal saline. Others advise administering the drug in 250 or 300 c.c. of physiologic salt solution. The authors believe that it is not important whether the drug be given in small or large dilution, but it is most essential that it be administered very slowly. Thirty minutes should be the minimal time allowed for the introduction of the drug into the blood stream. Obviously, it is easier to give larger dilutions slowly. This may be repeated every six or eight hours until the patient regains consciousness. Except in rare instances of idiosyncrasy to quinine, no unfavorable effects should result when it is properly administered. As soon as the patient's condition permits, the intravenous administration should be discontinued and oral treatment instituted.

Summary

1. The incidence of coma on admission to the John Gaston Hospital over a period of five years was 1.4 per cent. Malaria was seventh among the diseases responsible.

2. Malarial coma is more common in the autumn and is usually a complication of estivo-autumnal infection. This type of parasite is capable of occluding the capillaries of the brain, a quality not present in other plasmodia.

3. Our series of 48 cases is unique in that three of the patients were infected with only the plasmodium vivax (tertian malarial parasite). These three cases are briefly reported.

4. Coma is a serious complication of malaria. The mortality in our series was 40 per cent.

5. This complication may be prevented by adequate, early treatment. When coma develops it is best treated by quinine administered intravenously.

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EFFECT OF OXALIC ACID INTRAVENOUSLY ON BLOOD-COAGULATION TIME IN THREE HEMOPHILIACS *

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THE present conception of hemophilia [1] is that it is a constitutional disease characterized by prolonged hemorrhage, due to increased coagulation time. There is an inherited, sex-linked defect in the clotting mechanism. The typical finding is an increased coagulation time, which apparently results from a deficient supply of thromboplastin, which is in turn due to an abnormal resistance of the platelets to disintegration.

Quick [2] states that if thromboplastin is added, hemophilic blood will coagulate as rapidly as normal blood. This indicates that a deficiency of thromboplastin is the probable cause of the defective clotting, and that it is probably the slow liberation of thromboplastin from the platelets, rather than the absence of any factor essential for coagulation, that is responsible for the prolonged clotting time in hemophilia. In discussion of this, Birch [3] states that the important question is why the platelets do not break up. One group of workers believes that the mechanical resistance of the platelets to disintegration is actually increased, while another group holds that the platelets are normal, although placed in an abnormal environment, that is, hemophilic plasma.

W. H. Howell,[4] in the Wesley M. Carpenter Lecture (1938), stated that recent work furnishes good evidence for the view that blood plasma contains a specific substance which accelerates the process of clotting and which is present in smaller amounts in hemophilic blood. This substance is called "plasma thromboplastin" in the plasma, and "tissue thromboplastin" in the tissues. His experiments indicate that plasma thromboplastin is present in smaller amounts in hemophilic than in normal blood.

Other research [5] has suggested that in hemophilia there may be a deficiency in certain serum globulins and it has shown that a globulin substance prepared from normal human serum accelerates clot formation of hemophilic and normal blood, but that hemophilic blood serum lacks this property.

The control of hemorrhage in hemophiliacs has long been one of the most difficult conditions confronting physicians. At the present time, multiple blood transfusions offer most encouragement in the treatment of internal hemorrhage. If the bleeding occurs at some site (nose, mouth, throat, rectum, etc.) that can be reached locally, the use of coagulating snake venoms (Russell's viper [6] and fer-de-lance) is effective.

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Timperley [7] and his associates, in 1936, using an extract of egg-white parenterally, reduced the coagulation time and controlled hemorrhage in cases of hemophilia. They suggested it not as a cure for hemophilia but as a means of controlling the hemorrhage itself.

Lozner and Taylor [8] report that dialysis of cellular-free, citrated normal human plasma yields an euglobulin precipitate containing practically all of the clot-promoting activity of the plasma for hemophilic blood. This plasma euglobulin resembles normal human plasma in its ability when injected intravenously every six hours to maintain in hemophilia a reduced level of blood-coagulation time. Other preparations, such as sheep serum, pectin, ovarian hormones, and placental extract, have been suggested as useful in reducing coagulation time.

Oxalic Acid

In 1939, Steinberg and Brown [9] reported that they had prepared extracts from certain plants (shepherd's purse, wood sorrel, beets, oxalis, rhubarb, etc.) that accelerated markedly and rapidly the rate of coagulation of the blood. Subsequently, they identified oxalic acid as possessing most of the clotting power of the extract. Pure commercial oxalic acid was found to reduce the coagulation time after intravenous injection into rabbits. They established values for oxalic acid in the blood of human beings at 5.5 to 7.5 mg. per 100 c.c. Elevations in clotting time were attended by a fall in the blood oxalic acid, while reductions in clotting time conversely resulted in a rise in the oxalic-acid content of the blood.

Schumann [10] reports on the extensive clinical use of this oxalic-acid-containing plant extract (Koagamin) in the treatment of hemorrhage of various origins, hematemesis, bleeding gastric ulcers, jaundice, hemoptysis, hematuria, epistaxis, hemophilia, melena neonatorum and other forms of bleeding, with gratifying results. However, no case reports of its use in hemophilia are included. He states that the exact action of oxalic acid in the physiologic process of blood clotting is still problematic, but that it seems to act as a catalyzer and adds to the function of calcium, platelets, and tissue juices in the formation of thrombin.

Pharmacology of Oxalic Acid

Oxalic acid ($HOOC \cdot COOH \cdot 2H_2O$) is a dibasic acid and is one of the strongest of the organic acids. In the blood stream, it is probably changed immediately to an oxalate of sodium or calcium.

Oxalic acid and the oxalates possess a strong acid action, resulting in local irritation and corrosion.[11] Intravenously, in effective doses, they produce stimulation and later paralysis. Oxalic acid is probably a constant product of metabolism and possibly one of the functions of calcium is to render it harmless. Oxalates are resistant to oxidation in the animal body.

They are excreted by the kidneys. The smallest recorded fatal dose is 5 grams.

In a recent report [12] it was shown that glycogenolysis in the liver is completely inhibited by amounts of oxalates equivalent to only 10 per cent of the calcium present. Precipitated calcium oxalate had no effect on glycogenolysis. According to these results, oxalate acts directly on glycogenolysis and is detoxified by precipitation with calcium. Since oxalate is present in the liver in a concentration which affects the glycogenolysis, it is probable that oxalic acid has a physiological rôle. As both the indefinite substance called "prothrombin" and fibrinogen are presumably produced in the liver, it is possible that oxalate plays a part in their formation. Steinberg and Brown [9] have found that elevations in clotting time were accompanied by a fall in blood oxalic acid.

Method of Study

As several patients with hemophilia were available, it was decided to determine the effect of oxalic acid on their blood-coagulation time. The Lee and White method for coagulation time was used because it is considered the most accurate index of coagulation of venous blood. One c.c. of venous blood, carefully drawn to prevent presence of significant amounts of tissue juice, was placed in a test tube (8 mm. in diameter), which had previously been rinsed with physiologic salt solution. The tube was gently tilted at intervals. Coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot. By this method, the normal coagulation time is 5 to 10 minutes.

The oxalic acid solution used in this study contained 1 mg. oxalic acid C.P. per c.c. of distilled water and was sterilized by autoclaving at 15 pounds pressure for 20 minutes. The solution was stored in rubber-capped vials in the refrigerator until used. As the solution was highly acid, injections were all made intravenously at a slow rate.

Case Reports

Case 1. R. P., a white child 11 years of age, was admitted to the Hospital on December 2, 1939, complaining of pain in the left loin, extending into the groin. This child had been known to be a hemophiliac from the time he was six months old. His 12 previous hospital admissions were for hemophilic complications, namely, uncontrollable bleeding following injury, ecchymosis, synovitis, hematuria, etc. On examination, gross blood was found in the stool. He was treated by four transfusions, 250 c.c. each. The last one was given on December 9.

On admission, his red blood cell count was 2,600,000 and hemoglobin 6 grams. The gastrointestinal hemorrhage stopped a few days after the first transfusion, and his general condition responded satisfactorily. It was decided to try oxalic acid intravenously to determine what effect it would have on the coagulation time.

Because of the patient's insistence on going home for the holidays, he was discharged on December 22, with instructions to return to the Hospital soon after the first of the year for additional studies. Nothing more was heard from him until he was admitted as an emergency patient on January 8, 1940. On the day previous to ad-

mission, he had complained of pain in the legs, increasing weakness, nausea, and vomiting. No history of trauma was obtained. The patient was in profound shock, pale and pulseless. His heart sounds were extremely faint. He died 30 minutes after admission. The patient was in such an extreme condition that oxalic acid intravenously could not be given. An autopsy was performed January 9, 1940, by Dr. W. S. Waldron.

Autopsy showed a thin, emaciated, pale boy, with ecchymotic areas on both lower extremities. The right knee was swollen, and on incision into the joint cavity, fresh, fluid blood was obtained. The peritoneal cavity contained 1,100 c.c. of fresh, fluid blood. There was a massive clot filling up the entire free space on the left side of the

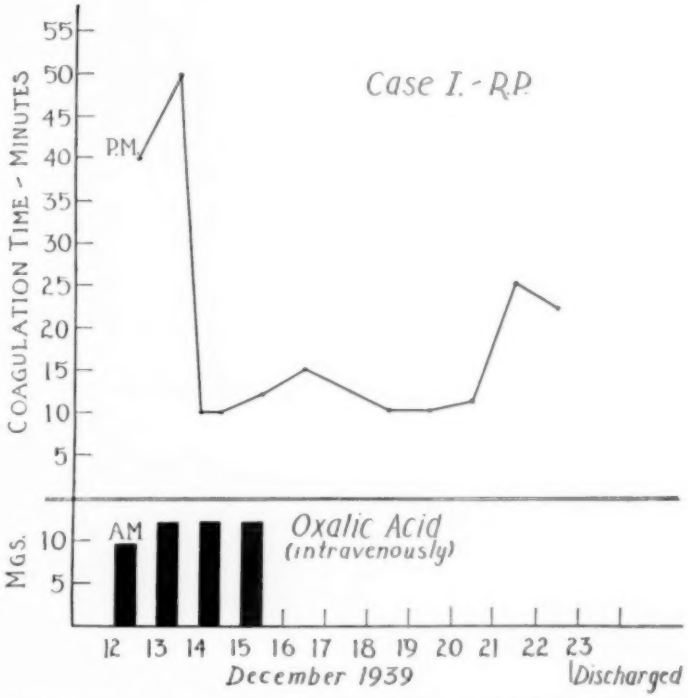

FIG. 1. Case 1. A total of 9 mg. (three injections of 3 mg. each) of oxalic acid was given on the first day (Dec. 12) beginning in the morning and the coagulation time determined in the afternoon (p.m.) was 40 minutes. On the second day after the first injection of oxalic acid the coagulation time was down to 10 minutes. The coagulation time remained between 10 and 15 minutes for one week.

Date (1939)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
12/12	40 (Afternoon)	9 (Morning)
12/13	50	12
12/14	10	12
12/15	12	12
12/16	15	
12/18	10	
12/19	10	
12/20	11	
12/21	25	
12/22	22	

abdomen and the pelvis. The clot was adherent to the descending colon, the capsule of the spleen, the left kidney, and extended into the muscular layer behind the left lumbar gutter. On further dissection, it seemed to originate from the psoas muscle, being intimately associated with the muscular fibers down to the edge of the pelvis and up to the muscular insertions in the vertebral column.

Case 2. J. M., male, white, 40 years old, has been a known bleeder all of his life.

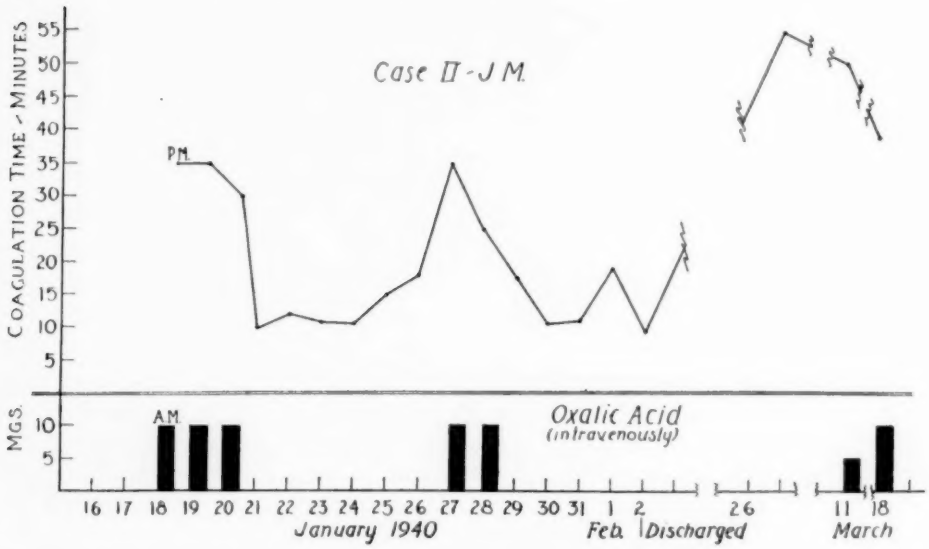

FIG. 2. Case 2. The coagulation time on admission was 50 minutes. In the afternoon, following the first morning intravenous injection of oxalic acid, the coagulation time was down to 35 minutes. On the third day following the first injection of oxalic acid the coagulation time was 10 minutes and remained less than 15 minutes for four days. Twenty-four days following his discharge from the hospital his coagulation time was 55 minutes (Feb. 26) and two weeks later (March 11) the coagulation time was 50 minutes at which time 5 mg. of oxalic acid were given. One week later (March 18) the coagulation time was 38 minutes.

Date (1940)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
1/16	50	
1/18	35 (Afternoon)	10 (Morning)
1/19	35	10
1/20	30	10
1/21	10	
1/22	11.5	
1/23	11	
1/24	16	
1/25	15	
1/26	18.5	
1/27	35	10
1/28	25	10
1/29	17.5	
1/30	11	
1/31	12	
2/1	14	
2/2	8	

He has had stiffness and swelling in his knees periodically for many years. His family history is negative except that his brother bled to death at the age of three. His previous hospital admission was on January 23, 1939, when he complained of hematuria and frequency of urination. At that admission his coagulation time (Lee-White) varied from 18 to 55 minutes, platelets were 120,000, and serum calcium was 8.8. Treatment consisted of blood transfusions.

After his discharge, he was followed by the Hematology Out-Patient Department and was given a course of sheep serum intracutaneously, with no change in the coagulation time. He was admitted to the Hospital January 15, 1940, for a course of oxalic acid intravenously to determine its effect on coagulation time.

Physical examination revealed a well-developed, well-nourished, white, adult male, with marked dental caries, and palpable liver-edge. These were the only physical abnormalities found.

Laboratory studies showed on January 16, 1940, a prothrombin time of 25 seconds (Quick's method); serum calcium 11.4; icteric index 4; blood sugar 95 mg. per cent; non-protein nitrogen 33 mg. per cent; urinalysis negative. On January 17, 1940, the bleeding time was three minutes, and clot retraction none after two hours, complete after 12 hours. On January 22, 1940, blood calcium was 11.3 mg. per cent; and three days later the non-protein nitrogen was 29 mg. per cent.

The patient was discharged from the Hospital on February 2, 1940. On subsequent return to the Hematology Out-Patient Department, February 26, 1940, the coagulation time was 55 minutes. On March 11, 1940, the coagulation time was 50 minutes, and the patient was given 5 mg. of oxalic acid intravenously. One week later (March 18) the coagulation time was 38 minutes and oxalic acid, 10 mg., was given intravenously.

Case 3. F. S., a white, male child, aged six, has been known to be a bleeder all of his life. He has a younger brother who is also a hemophiliac. He has been admitted to the Hospital on four occasions for hemophilic manifestations, such as hematuria, ecchymosis, and synovitis. The coagulation time during these various admissions has varied from 70 minutes to three hours. The treatment has consisted of transfusions and, following this, the coagulation time has been reduced to somewhat normal limits (on one occasion seven minutes). He was admitted to the Hospital on January 16, 1940 so that the response of his coagulation mechanism to oxalic acid intravenously might be studied.

Laboratory studies, on admission to the Hospital (January 16, 1940), showed 4,280,000 red blood cells and 12 grams of hemoglobin. There were 7,800 leukocytes, of which 58 per cent were polymorphonuclear cells, 38 per cent lymphocytes, and 4 per cent mononuclear leukocytes. The icteric index was 3; the serum calcium 11.8 mg. per cent serum; blood sugar 83 mg. per cent; and non-protein nitrogen 28 mg. per cent.

On January 17, 1940, the bleeding time was three minutes, the prothrombin time 35 seconds (Quick's method), and clot retraction, which began in two hours, was complete in 12 hours. Calcium was 10.6 mg. per cent on both January 23 and January 31, 1940.

The blood count of February 5, 1940 showed 4,350,000 red blood cells and 12.5 grams of hemoglobin. There were 6,900 leukocytes, of which 63 per cent were polymorphonuclear cells, 34 per cent lymphocytes, and 3 per cent mononuclear leukocytes. Urinalysis was negative; bleeding time was three minutes; prothrombin time 30 seconds; and clot retraction was complete in two hours.

On February 6, 1940, the blood sugar was 91 mg. per cent, and non-protein nitrogen 26 mg. per cent.

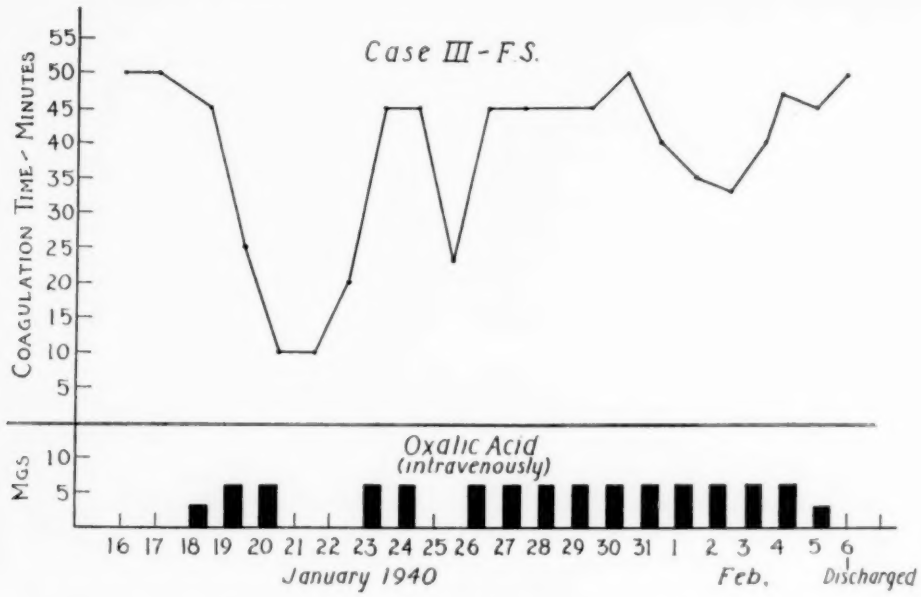

FIG. 3. Case 3. Coagulation time before oxalic acid was given was 50 minutes. On the third day of oxalic acid therapy the coagulation time had decreased to 10 minutes. After three days of no oxalic acid the coagulation time had risen to 45 minutes. Following this he was refractory to further injections of oxalic acid.

Date (1940)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
1/16	50	
1/17	50	
1/18	45 (Afternoon)	3 (Morning)
1/19	25	6
1/20	10	6
1/21	10	
1/22	20	
1/23	45	6
1/24	45	6
1/25	23	
1/26	45	6
1/27	45	6
1/28		6
1/29	45	6
1/30	50	6
1/31	40	6
2/1	35	6
2/2	33	6
2/3	40	6
2/4	47	6
2/5	45	3
2/6	50	

Discussion

The intravenous use of oxalic acid caused the coagulation time in three hemophilic patients to fall to the upper limits of normal, that is 10 minutes, in two to three days (Cases 1 and 3, two days; Case 2, three days). Oxalic acid was not given again in Cases 2 and 3 until the coagulation time had increased to 35 and 45 minutes, respectively. On resumption of oxalic-acid therapy, Case 2 responded in three days with a reduction in coagulation time to 11 minutes. On a second course of oxalic acid, Case 3 failed to respond.

There was no indication in any of the patients that oxalic acid caused toxic manifestations. The serum calcium in Case 2 remained approximately the same, while in Case 3 the serum calcium was reduced from 11.8 to 10.6 mg. after a total of 57 mg. of oxalic acid had been given over a period of 14 days.

The modus operandi of oxalic acid in reducing the coagulation time in hemophilia is unknown. One of the most likely possibilities is that by disturbing the physico-chemical relationship, it decreases the platelets' resistance to disintegration. The surface tension of the platelet membrane may be altered so that thromboplastic material is more readily released. The elucidation of this mechanism will undoubtedly furnish important information as to some of the controlling factors in blood coagulation.

From figures 1, 2, and 3, it is apparent that the reduction in coagulation time is quite transient, indicating that whatever is altered in the coagulation mechanism rapidly returns to its original state. The reaction in Case 3 in responding significantly to the first series of injections of oxalic acid and not to a subsequent series would indicate that the coagulation mechanism was able to compensate for the presence of oxalic acid.

Results

Limited studies on three hemophiliacs indicated that intravenous oxalic acid quickly reduced their blood-coagulation time. The rapid return to prolonged coagulation time after its administration suggests that oxalic acid does not constitute a cure for hemophilia. However, it would seem to be valuable as a measure in attempting to control bleeding in hemophilia. For this emergency therapy, oxalic acid, 5 mg., in sterile solution, can be given intravenously two to three times daily for several days.

Summary

1. Three hemophiliacs with prolonged coagulation times were given oxalic acid intravenously and their coagulation times studied.

2. The coagulation time of each decreased to normal in two or three days.

3. Oxalic acid was then stopped, following which the coagulation time increased at different rates in the three cases (Case 1, 22 minutes after seven days; Case 2, 35 minutes after six days; and Case 3, 45 minutes after three days).

4. The modus operandi of the decrease in coagulation time is not known.

5. No evidence of toxicity was present in any of the three patients who received oxalic acid intravenously.

6. There is no indication that oxalic acid can be considered as a cure for hemophilia. It would appear, nevertheless, that its use, along with other known beneficial measures, notably multiple transfusions, would be warranted in attempting to control bleeding in hemophilia.

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THE PREVENTION OF ARTHRITIC DEFORMITIES BY EARLY ORTHOPEDIC MANAGEMENT *

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ORTHOPEDIC surgery provides many excellent reconstructive operations for overcoming the crippling deformities of arthritis.[1, 2, 3, 4] Whenever the writer has had to treat a patient by an arthrodesis or the reconstruction of a joint, the need has been apparent for an effort on the part of the medical profession [5, 6] to prevent the deformities requiring such procedures. Thereby, patients whose vitality is already depleted by the ravages of a chronic systemic disease would be saved from submitting to major operations. The need for a concerted effort to preserve normal joint structure and function becomes more evident in view of the fact that *the average deformity in the average arthritic could have been prevented.*

Of paramount importance in the care of a patient with arthritis, if he is to be saved from a state of partial or total invalidism, is the institution of *early orthopedic management.* By early orthopedic management, the muscle strain and the traumatic joint irritation [7, 8] due to faulty body mechanics are overcome. By early orthopedic care, contractures are prevented, or if slight distortions are already formed, correction is established before they become fixed deformities. At the same time, orthopedic care provides for placing acute joints mechanically at rest, affording relief from pain. Orthopedic management should be instituted as soon as the diagnosis of arthritis is made,[5, 9, 10] and the attending physician should not wait until deformities are well advanced before he provides his patient with orthopedic help.

Sufficient emphasis is not placed on orthopedic management in the early stage of arthritis, although there is widespread appreciation of the value of orthopedic treatment late in the disease. In fact, practically everyone who has contributed to the literature on this subject has indicated the importance of orthopedic care in arthritis. Yet, with such general recognition of the value of this treatment, serious deformities (figure 1) are seen, which could have been prevented if simple orthopedic measures had been used at the onset of the illness. The statistics on the economic loss [11] and human suffering from arthritis [12, 13] are appalling, but so few are cognizant of the basic cause that no substantial effort is made to combat it. The explanation of the development of such deformities would seem to lie in the failure to appreciate the fact that orthopedic care must run *concurrently* with medical care [14, 15] from the time that the diagnosis of arthritis is made.

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The attitude of the attending physicians, as well as that of the patient, accounts to a certain extent for the lack of complete care of the patient suffering from arthritis.[16] Although there is perhaps no disease which requires the therapeutic assistance of so many branches of medical practice [17] as does arthritis, the burden of responsibility rests squarely and equally on the shoulders of the internist [5] and the orthopedist. It is their joint duty to meet the problem and cope with it to the best of their ability. The internist rightly recognizes arthritis to be primarily a medical disease belonging to his specialty, whereas the orthopedic surgeon considers joint involvement as his own domain. Both the internist and the orthopedist must realize that arthritis is not his sole possession and they must appreciate that the control of this disease calls upon their *combined effort.*

FIG. 1. (*Left*) Preventable deformities.
FIG. 2. (*Right*) "Comfortable position" encourages deformities.

In the mind of the patient, "rheumatism" is such a common ailment that it is difficult to make him believe that early pain and swelling of one joint may be the first sign of a disease that can involve his entire body and result in total disability. The patients must be educated to realize the importance of the first signs of the disease and the necessity for prolonged treatment [18] by whatever special methods of therapy they individually require. The coöperation of the patient, the internist, and the orthopedist is needed in the effort to solve the problem of the treatment of arthritis.

In order to approach the subject of orthopedic management intelligently, it is necessary to have a thorough understanding of the nature of the deformities that develop in arthritis. Table 1 is self-explanatory, but it should be emphasized that deformities are not simple entities limited to a single joint; rather, deformity progresses [19] and one deformity leads to the development of more serious secondary, complex deformities.

When a joint is inflamed, the muscles controlling the joint contract in order to prevent not only active motion, but also that caused by the nursing

TABLE I

The Common Deformities

Spine	Flexion with rotation
Shoulders	Adduction with internal rotation
Elbows	Flexion (30–40°) with pronation
Wrists	Flexion with ulnar deviation
Fingers	Flexion
	(*a*) Ulnar deviation
	(*b*) Atypical extension
Hips	Flexion and adduction—precipitating
	(*a*) Equinus, flexion of knee, knock knee and flat foot
	(*b*) Tilting pelvis
	(*c*) Increased lumbar lordosis
Knees	Flexion
	(*a*) Precipitating equinus which encourages abduction and external rotation of hip, followed by flat foot, knock knee and finally tilting of pelvis to shortened side
	(*b*) Posterior dislocation of tibia
Feet	Equino-Valgus
	(*a*) Midtarsal pronation
	(*b*) Depressed anterior arch
	(*c*) Hammer toes
Jaw	Closed

care or even by the jarring of the bed. Muscle balance is such that in practically all joints the flexor or adductor muscles are the stronger. For this reason painful joints are usually found in flexion and adduction. This is demonstrated by figure 2, which shows a patient with moderately severe rheumatoid arthritis holding his shoulders in adduction and internal rotation, his elbows flexed and pronated, and his wrists and fingers in flexion and ulnar deviation. These positions of deformity are the comfortable positions[6] which are assumed by the patient, and unless precautionary measures are taken the "comfortable position" leads to disaster. Several factors assist muscle contraction in the development of deformities. These include the sagging of the bed, the pressure of the bedclothes, static influences, muscle strain and gravity.

With these introductory remarks, let us see, by studying specific examples, precisely what orthopedic management means. The writer believes that if the principles to be suggested are followed, the large majority of deformities will be prevented, thereby reducing to the minimum the necessity for manipulation and open operations.

Inflamed and painful tissues demand rest.[20, 21] People suffering from arthritis should spend much of their time in bed.[10] Therefore, the patient's bed is of primary consideration. If several pillows are used under the head, the cervical and dorsal spine is forced into forward flexion. A sagging spring (figure 3) and soft mattress cause increased flexion of the dorsal spine with strain on the posterior spinal ligaments and compression of the anterior portions of the vertebral bodies and intervertebral structures. The lumbar spine becomes straight or even kyphotic, causing undue strain on the posterior spinal ligaments and the muscular and fascial supports of the back. The hips are forced into flexion, causing a contraction and shortening of the powerful ilio-psoas muscles and the Y ligaments of the joint capsules.

The knees are forced into hyperextension, causing strain on the posterior joint capsules and the posterior muscles of the thighs and calves. Such strain results in a traumatic irritation of the structures involved.

A firm bed, as shown in figure 4, is obtained by placing a one-inch thick board directly under a mattress of medium thickness. The board should extend the full length and breadth of the bed. When this firm bed is used, and one thin pillow placed under the head, and a slight support such as a folded towel or small pillow placed under the back to maintain lumbar lordosis, the strain caused by the sagging mattress is avoided. At first the patient may object to the hard bed, but he soon becomes accustomed to it

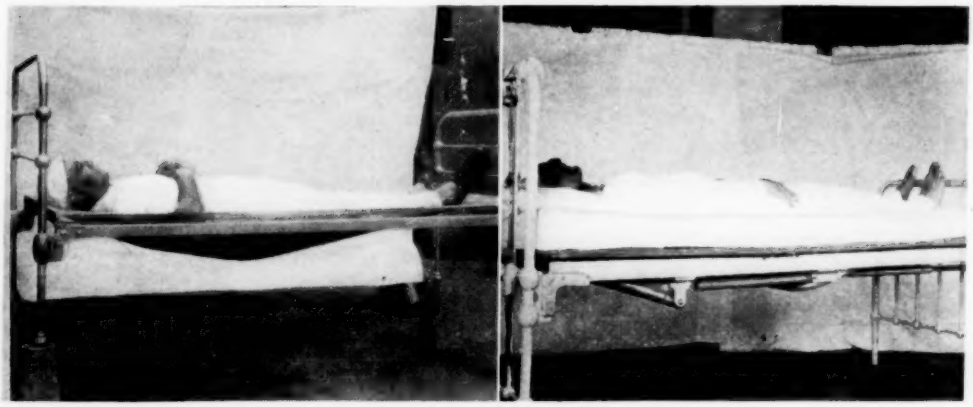

FIG. 3. (*Left*) Sagging bed causes deformities and soft tissue strain.
FIG. 4. (*Right*) Firm bed permits normal body alignment.

and finds that he is more comfortable with relief from soft tissue strain. If the patient feels the need of lateral support, pillows or sandbags may be placed along each side of the body. Patients should be discouraged from lying on their sides (shoulder and hip) as this causes severe lateral deviation of the spine. The lateral oblique position (resting on buttocks and scapula with a supporting pillow behind the back) avoids distortion and soft tissue strain and frequently affords the patient considerable rest and relaxation. (For discussion of optimum positions for function, see Timbrell Fisher [22] and Anopol.[23])

The next important consideration is the arrangement of the bed clothing. A "cradle" is used universally to keep the pressure of blankets off painful joints, but few realize that "cradles" must also be used to prevent the pressure of bedding from holding the lower extremities in abnormal positions. The average person lying in bed allows his hips to rotate externally (figure 5), his knees to flex slightly, and his feet to go into mild equinus. If the bedding is pulled firmly over the limbs in this position, the simple distortions will advance to almost fixed deformities. The severe deformity noted in figure 6 is a result of the pressure from bedclothes, which rotated

the feet at right angles to the legs. A "cradle" avoids such pressure as well as facilitates the use of sandbags or splints to hold the extremities in correct alignment. An electric lamp can be suspended from the frame of the "cradle" to provide warmth or therapy.

The spine is the most important structure from the standpoint of preserving normal relationship, because if the spine becomes fixed in its typically deformed position of flexion and rotation, surgery cannot correct it. The firm bed with one pillow under the head and a small support to maintain lumbar lordosis will go far toward preventing spinal deformities. However, if there is a tendency for the dorsal kyphosis and the flexion of the hips to increase, small supports (such as a folded towel or a small pillow) can be used at the point of maximum kyphosis[9] and under the sacrum. This simple means (demonstrated in figure 7) will soon correct both the kyphosis and the tendency to hip flexion. At first, the supports should be

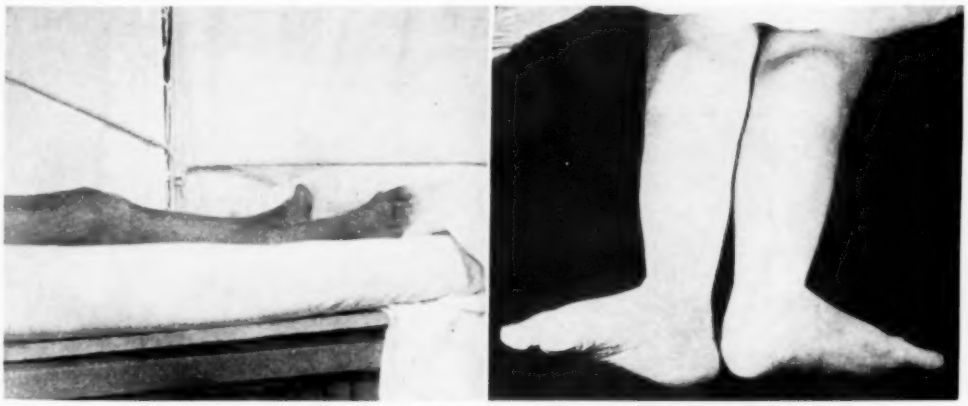

FIG. 5. (*Left*) Usual position of lower extremities when resting.
FIG. 6. (*Right*) Deformity caused by pressure of bed clothes.

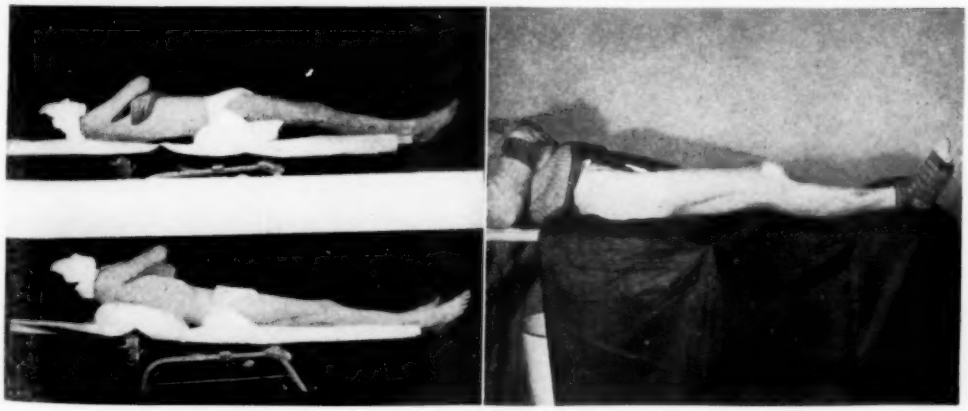

FIG. 7. (*Left*) Effective method of extending hips and back.
FIG. 8. (*Right*) Posterior dislocation of tibia on femur caused by pillow under thigh.

very thin to avoid undue strain, but they can be gradually increased in thickness. A support as large as the pillows shown in the illustration is rarely needed and should be used only under close supervision. If flexion of the spine is prevented, there is little danger of the development of scoliosis.[24]

The hips should be considered in connection with the spine because deformities in these structures go hand in hand. Distortion in the trunk changes the line of gravity and necessitates flexion of the hips. Similarly, a fixed flexion deformity of the hips causes a forward tilting of the pelvis which in turn precipitates that extreme degree of lumbar lordosis which invariably accompanies flexion of the hips. A pillow placed under the sacrum as noted above is usually sufficient to control the early tendency to hip flexion.

Rotation and adduction deformity of the hips is quite another matter. The lower extremities should be held in a position midway between internal and external rotation, and at frequent intervals the thighs should be separated so as to avoid contraction and shortening of the strong adductor muscles. These positions are maintained by sandbags or, when necessary, by splints. All forces used to prevent deformities in the hips should be exerted above the knees because any force exerted at the foot or leg will first have to act through the ankle and knee joint, thus losing considerable effectiveness and putting strain on the ankle and knee supports. In the acutely inflamed hip, a short period of immobilization in a plaster of Paris spica will do much to prevent threatened deformity.

It can be said without hesitation that the knees are the most important of the large joints to consider from the standpoint of the prevention of deformities. This is true because they are so universally involved and so frequently abused. The most common mistake is to allow the patient to lie with a pillow under his knees in an effort to relieve his pain. This flexion of the knees rapidly causes a fixed contraction of the posterior capsules and the hamstring muscles. The patient who walks on a flexed knee joint precipitates distortion in both lower extremities and throughout the trunk. As a rule, pillows that are used to relieve the pain in the knees are placed under the thighs and not under the legs. The supporting structures of the acute joints are weakened. Hence, the weight of the tibia stretches the muscles and the joint capsule, allowing the tibia to become posteriorly displaced on the femur (figures 8 and 9). The posterior displacement of the tibia causes a deformity which resists correction more than any distortion of the large joints. This whole chain of circumstances can be prevented by complete immobilization of the involved lower extremity in circular plaster of Paris casts until the acute inflammation has subsided, and then a posterior splint or appropriate brace can be used to maintain the correct position.

The ankles and the feet are the next joints to be considered. While patients are in bed, splints are used to maintain the feet and ankles in normal dorsi-flexion and inversion. When the patient becomes ambulatory, the footwear should be such that it maintains the correct alignment of the feet, ankles and knees.

The multiple distortions and the strain of supportive soft tissues caused by weak feet should be given adequate consideration in all stages of arthritis. Such strain causes fatigue and is an important factor in increasing the disability in the ambulatory stage of arthritis. The anatomical alignment of the superstructure (the trunk) is dependent upon the sturdiness of the foundation (the feet). Figure 10 shows the normal weight-bearing line [25] in the lower extremities, while figure 11 is the same patient before her

FIG. 9. Roentgen-ray of tibial dislocation shown in figure 8.

FIG. 10. (*Left*) Patient with normal weight bearing line.
FIG. 11. (*Right*) Weak feet cause strain on tarsal and ankle joints and result in knock knees.

weak feet had been corrected. It will be seen in the latter picture that the eversion and valgus of the feet caused a strain [26] on the ankle and tarsal joints. In addition, the eversion precipitated bilateral knock knees with the resultant strain on the internal lateral ligaments and capsules [27, 28] of the knee joints. It is readily seen that in the early stages of the disease the traumatic irritation caused by these distortions provides a fertile field for the advancement [22] of rheumatoid arthritis. Again, when the patient bears weight following acute attacks, the soft tissue strain retards the subsidence of the inflammation in joint tissues.

The treatment for the correction of weak feet is tedious, but not difficult. While the feet are still malleable, treatment should be started by strapping the feet in dorsi-flexion and inversion for a period of 10 days. Then foot plates (if needed) and correct shoes are worn. Corrective exercises and attention to proper walking posture complete the treatment.*

In the wrists and hands the deformities to be guarded against are flexion and ulnar deviation (figure 12) with hyperextension at the proximal interphalangeal joints. The method of preventing deformity in the wrists and fingers consists of complete immobilization during the painful stage followed by the use of a removable anterior splint, such as is shown in figure 13.

FIG. 12. (*Left*) The early distortion in wrists and fingers.
FIG. 13. (*Right*) Molded splint to prevent the deformity seen in figure 12.

This splint extends from the elbow to the fingertips and is slightly "cocked up" at the wrist. A flange on the ulnar side prevents ulnar deviation. Active use and appropriate physical therapy [29] can be used in conjunction with the splint.

In cases in which measures of prevention are not instituted, deformities begin to develop early. The first sign of oncoming deformity is the inability, at examination, to place the joint in the position opposed to the deformity. For example, in the case of the wrist and the hand, when the doctor finds that full extension and radial deviation are no longer present,

* For details of treatment for weak feet see Anopol [30] and Stump.[25]

he can anticipate that flexion and ulnar deviation will soon be definite deformities.

Distortions can be controlled by simple methods. If the joints are so painful that even slight motion causes distress, a short period of complete immobilization of perhaps from five to seven days may provide sufficient relief to permit active and passive motion. The joints should be immobilized in the position in which the doctor finds them, and *circular* plaster of Paris casts, or one of the newer substitutes [31] should be used. When the plaster is applied with gentleness and care, anesthetics are not necessary. Let us consider an adducted, painful shoulder with the arm held to the side of the body. When pain has subsided sufficiently to permit motion, the arm should be abducted [32] gradually by placing supports between the arm and chest wall. The abducted arm can rest against these supports without the active use of the patient's own muscles. In like manner, the flexed elbow can be extended and supinated gradually. When active motion can be carried out without pain, a device such as that shown in figure 14 can be

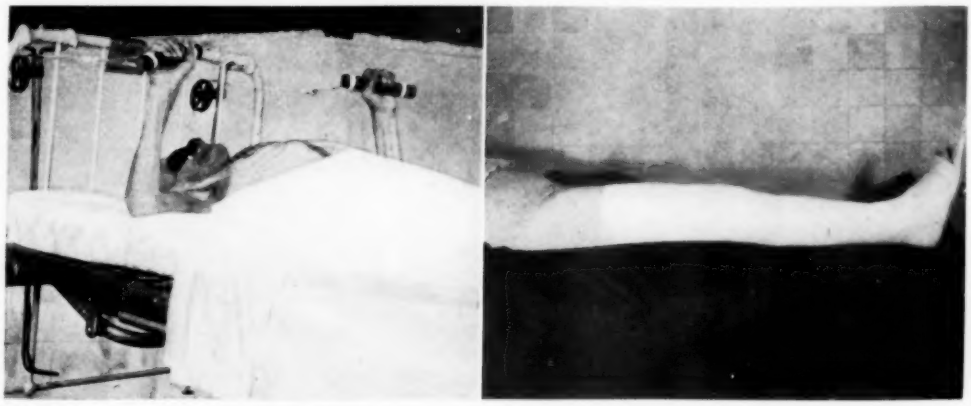

FIG. 14. (*Left*) Simple apparatus increases motion and respiration.
FIG. 15. (*Right*) Acutely inflamed joint completely immobilized in cast.

used to encourage active abduction. Such a method of exercising not only overcomes the tendency to fixed deformity, but also encourages muscle development and can be used as an exercise for respiration.[9] The use of the apparatus increases motion in all the joints of the upper extremity. It is important to see that the patient actually abducts his shoulders and not merely goes through the easier movement of forward flexion.

COMPLETE IMMOBILIZATION OF JOINTS

It might be well to comment on the complete immobilization of acute joints. Many doctors feel that complete immobilization results in ankylosis. This is not true.[33] If ankylosis takes place, it is the result of the inflammatory process causing a destruction of the articular cartilage. Im-

mobilization in circular plaster puts the inflamed joint at rest [34] and favors a subsidence of the inflammation, thereby actually preventing destruction of the joint. A word of caution [10] is necessary in the use of immobilization. Joints should not be immobilized indefinitely, but rather for periods of from five to seven days. If necessary, casts can be reapplied, but the joints should be inspected at short intervals. Figure 15 shows an acute knee which was completely immobilized for one week. At the end of three weeks, by means of active motion alone, the patient had gained full flexion of his knee joint, as seen in figure 16. Circular plaster of Paris can be used with impunity in the treatment of acute joints, provided the care is thoroughly *supervised* during the period of immobilization.

Another advantageous use of immobilization of joints is demonstrated in figures 17, 18 and 19. The patient, a chronic rheumatoid arthritic, had

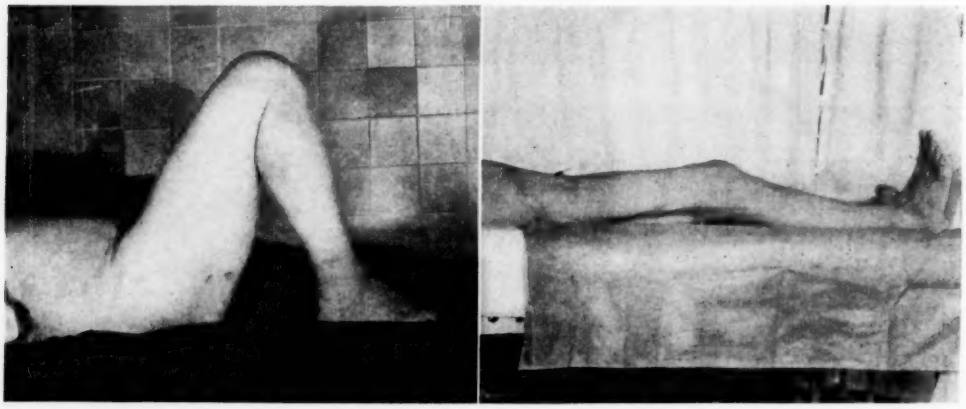

FIG. 16. (*Left*) Same knee as in figure 15; three weeks later. Immobilization encourages return of function.
FIG. 17. (*Right*) Flexed knee due to muscle spasm of months' duration.

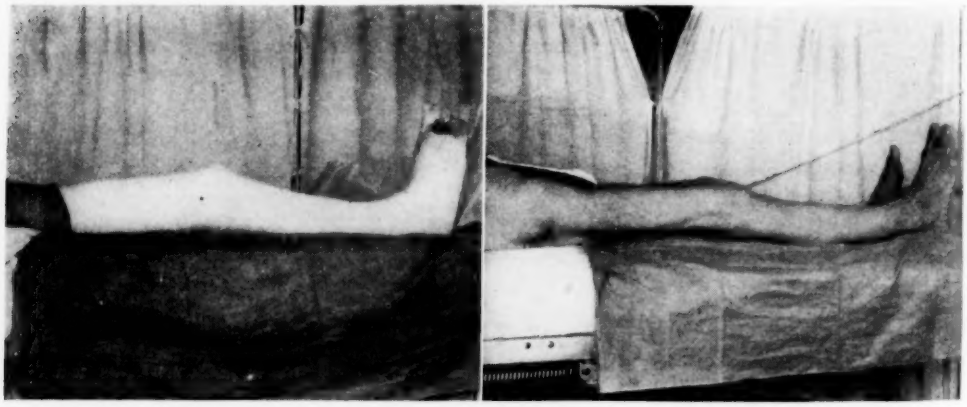

FIG. 18. (*Left*) Same knee as figure 17. Flexion maintained. Immobilized for rest and comfort.
FIG. 19. (*Right*) Four days later. Same as figures 17 and 18. Rest alone makes extension possible.

had a flexion deformity of the knee for many months. The contracture was due to a spasm of the hamstring muscles in response to the pain in the knee. The lower extremity was immobolized *maintaining* the flexion. The immobilization relieved the pain in the joint, obviating the necessity for muscle spasm. The cast was removed at the end of four days and without manipulation the knee immediately took the position of full extension. A posterior molded splint was used at rest periods to maintain the extension. When the flexion contracture is greater than shown in this case it might be necessary to use repeated casts, obtaining a little more extension with each cast until full correction is obtained. The advantages of this treatment are that it does not cause pain or the muscle pull from traction, and it saves the patient from manipulation or open operation. Primarily, this procedure avoids any damage to the joint structures.

After Care

If the above procedures are followed, much can be done to prevent the crippling sequelae [35] of chronic arthritis. However, treatment must be continued until the patient can be considered completely recovered and back to normal life.

For the patient who has recovered from the acute stage of arthritis, one must think of preparing his muscles [36] to do the added work required by weight-bearing when he becomes ambulatory. Massage of the back and of the muscles above and below [37] the joints is of primary importance in the development of muscle tissue and muscle tone. Massage should at first be very gentle and should be controlled by the patient's reaction of pain and fatigue. The massage should be given by a well-trained technician under the direct supervision [32] of the attending doctor. Active motion,[38, 39] either under water [40, 41] or with the patient in bed, has the double benefit of increasing mobility and muscle development. Passive motion is a form of manipulation and should be used only in special cases. When the patient first starts to walk, it is essential that he have proper footwear to maintain the correct alignment of his lower extremities [35] as well as an adequate brace to control any joint that is not yet capable of self-support. If a brace is required for the back, it must be at least long enough to control the pelvis and the lumbar and low dorsal spine.

When the patient is beginning to bear weight, there is a great tendency for body distortions to develop and he will have to be carefully guarded to see that at this stage [18] a deformity of one or more joints does not develop. Any indication of impending deformity should be given immediate attention and treated as in the acute stage of the disease.

Conclusions

The average deformity in the average arthritic can be prevented by the institution of orthopedic management in the early stage of the disease. Co-

operation between the internist and the orthopedist, who are primarily responsible for the care of these patients, is needed to insure concurrent orthopedic and medical care from the time the diagnosis is made.

Orthopedic management is based upon a thorough understanding of the nature and development of deformities in chronic arthritis. It requires a knowledge of basic orthopedic principles.

In this paper the orthopedic care required to prevent the development of deformity in each joint has been discussed. The correction of mild distortion has been outlined. The observation of the patient over a long period, particularly when he becomes ambulatory, is emphasized. If the principles of treatment that have been presented are followed, the great majority of patients suffering from arthritis will be spared the misfortune of the development of disabling deformities.

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CARDIAC ANEURYSM

A Report of Ten Cases *

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INTRODUCTION

CARDIAC aneurysm is not a rare finding on postmortem examination. Clinicians of the older generations were well aware of this and, in view of the seriousness of the condition, their eager search for clinical signs and symptoms by which it might be recognized during life was easily understandable.

Beginning with the middle of the last century, numerous medical reports are available, referring particularly to the findings by physical examination. Huchard [1] suggested that a very large area of cardiac dullness in subjects affected by arteriosclerosis might point towards the existence of a cardiac aneurysm. Abnormal sounds and musical murmurs, humming, blowing or whistling, either systolic or diastolic, were repeatedly mentioned as valuable aids to diagnosis. Their presence was attributed to the flow of blood through a narrowed opening leading into the aneurysmal sac. Huchard thought that a post-systolic murmur audible only over the apical region, in association with certain other physical signs, was a useful sign in the diagnosis of cardiac aneurysm. Also a gallop rhythm was often mentioned as indicative of this condition. Lutembacher [2] stressed the significance of a continuous, rather severe pain limited to a well defined area in the apical region. Pulsatory phenomena, as obtained by palpation, have played a considerable part in all diagnostic inquiries. Kasem-Beck [3] stated that a heavy cardiac thrust, associated with a feeble pulse, was a reliable sign in diagnosis. Huchard [1] described, as a characteristic finding, an intensified cardiac thrust particularly marked over the precordium but absent in the apical region.

In spite of all these observations some of the eminent clinicians have repeatedly expressed very skeptical opinions as to the diagnostic value of the signs reported. Hall [4] wrote in 1903: "Aneurysm of the heart must necessarily be of interest rather to the pathologist than to the clinician, for they are outside of the pale of practical diagnosis." Sternberg [5] stated in 1914 that out of 300 cases published up to the time at which he was writing, only two had been diagnosed during life. Hence he concluded that physical signs were worthless in diagnosis of cardiac aneurysm. Lutembacher [2] held the same view, and Christian and Frick [6] wrote in 1922: "The diagnosis of

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partial cardiac aneurysm by means of palpation, auscultation and percussion is generally and rightly considered to be impossible." Strandell[7] in 1930 likewise stressed the impossibility of detecting cardiac aneurysm by means of physical diagnosis, and stated: "As a rule one does not even think of it, when dealing with a case of heart disease."

One may rightly ask why so many very valuable observations in the field of physical diagnosis have been of so little avail in the diagnosis of the condition. The answer is that one important premise for the diagnosis was missing as yet; namely, clinical knowledge of cardiac infarction, which knowledge has been available only during the last 15 years. More recently the question has been approached again by radiologists and clinicians, and considerable progress has been made in the diagnosis of cardiac aneurysm. This has been the result mainly of proper physical examination, and only to a lesser degree of radiological examination. It is true that the radiologist has in some cases revealed definite findings which have been reliable signs for the presence of an aneurysm. We refer to a well defined bulge along the left border of the cardiac silhouette, sometimes associated with a systolic lateral pulsation over this area. A number of cases are available in which a diagnosis was thus established.[8, 9, 10, 11, 12, 13, 14, 15] On the other hand, those who have been interested in this subject have come to realize that characteristic radiological changes are often missed in the presence of aneurysm of the left ventricle. The reason for this will be discussed later.

The value of physical signs for recognition of cardiac aneurysm has been stressed increasingly, and palpable pulsatory phenomena of the chest wall have taken a prominent place. Great importance was attributed by Libman and Sacks[16] to the association of a feeble first sound and a pulsation most marked between the apex of the heart and the sternum. East[8] described two cases of cardiac aneurysm in which a diagnosis was made principally through the observation of a "wavy pulsation" above and inside the left nipple. The diagnosis was corroborated by the radiological study. Erlsbacher and Scherf[17] likewise reported on pulsatory findings which enabled them to diagnose cardiac aneurysm in three cases. These writers stressed the importance of an early retrogression of the pulsation, which had appeared within a few days following the coronary artery occlusion and had receded, in two cases, several weeks later when a firm scar had displaced the necrotic heart muscle tissue.

We have studied the clinical symptomatology of cardiac aneurysm mainly on the basis of pulsatory phenomena, and have been able to diagnose 10 cases during life in the course of the last four years. In the following report we want to outline the signs which have proved useful for the recognition of this important and not infrequent cardiac lesion.

Case Reports

Case 1. H. F., male, aged 64. For the preceding five years the patient had experienced painful oppression in the cardiac region and respiratory effort limitation

when climbing mountains. In May 1935, while travelling on the train, he felt a constricting cardiac pain, which radiated between the scapular regions and lasted for a quarter of an hour. Two months later a similar attack of pain occurred, coming on at night time, and lasting for several hours; a third attack of pain made its appearance two weeks later, and was followed by unconsciousness. The patient was brought to the hospital and a diagnosis of cardiac infarction was made. The recovery was very slow, and the patient was readmitted to the hospital three months later.

Clinical examination: During systole one could observe a definite systolic propulsion, most marked at the level of the fifth rib, between the left midclavicular and the left parasternal line (figure 1). This pulsation extended slightly beyond the left mid-

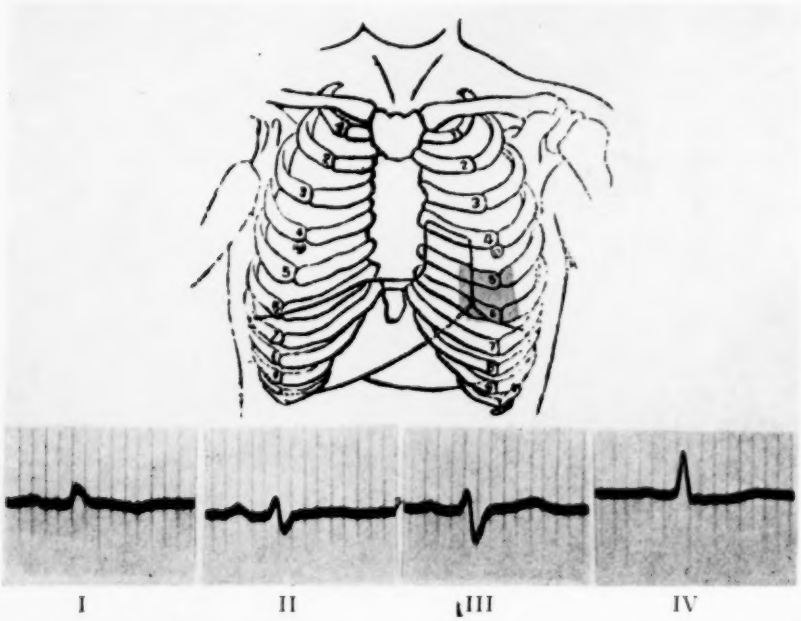

FIG. 1. Case 1. *Above:* Scheme of chest. The shadowed area indicates the extent of the precordial pulsation. *Below:* Electrocardiogram with the three limb-leads and the precordial lead (IV). In the latter the galvanometer connections are so made that relative negativity of the exploring electrode is represented by an upward deflection.

clavicular line and caudad to the sixth rib. The heart sounds were of low intensity, and no murmurs were heard. The heart rate was 64 per minute, and the rhythm was regular. Blood pressure varied between 95 mm. of mercury systolic with 95 diastolic and 80/50. Electrocardiographic findings (figure 1): Sinus rhythm was present, and the voltage in all leads was diminished; a well marked S deflection was noted in Leads II and III and a small R in Lead I. T in Lead I was slightly negative, and the R–T segment showed a slight elevation. In the chest lead * the initial downward stroke was absent, and T was flat positive. Radiological study: No changes characteristic of cardiac aneurysm were noted. Orthodiagram (figure 2) revealed a moderate degree of cardiac enlargement, with the oblique diameter measuring 15.5 cm. The amplitude along the left lower contour, as observed fluoroscopically, was exceedingly small. The

* The chest leads were taken in this and in the following cases from the apex region and the left leg; the right arm cable was connected with the precordium, the left foot cable with the left leg, so that relative negativity of the exploring electrode was represented by an upward deflection.

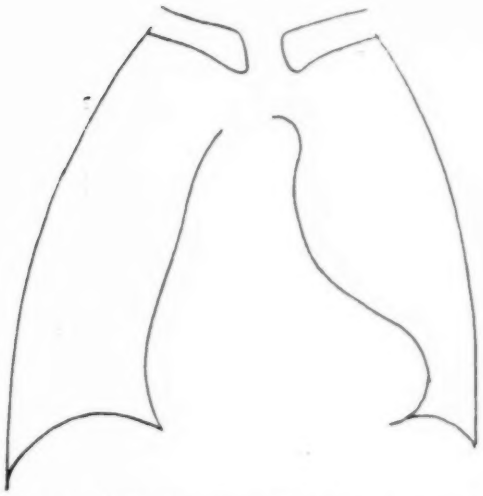

FIG. 2. Case 1. Orthodiagram indicating some widening, corresponding to the lower portion of the left ventricle. No circumscribed bulge is visible.

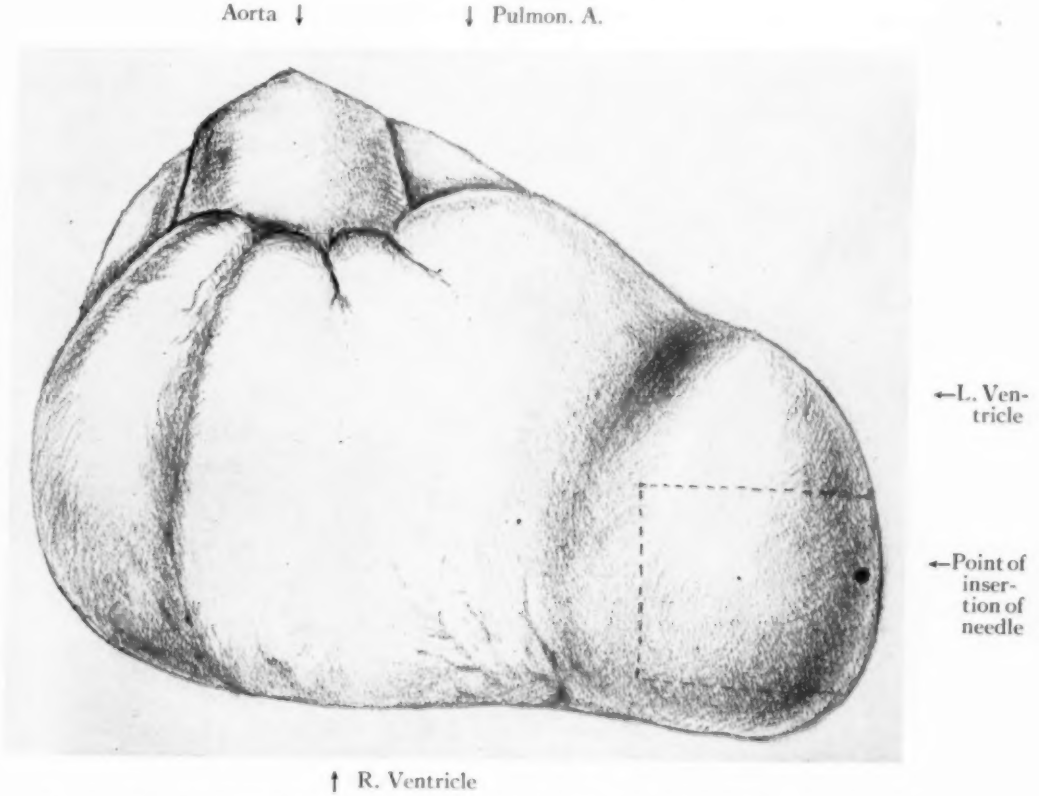

FIG. 3. Case 1. Drawing of the heart in situ. Note the large bulge along the ventral portion of the left ventricle. The broken line indicates the corresponding area of pulsation as it was noted during life.

rest of the clinical examination was negative. The urine analysis revealed nothing abnormal, and the Wassermann reaction was negative.

On the basis of the peculiar precordial pulsation we diagnosed aneurysm of the heart, involving the ventral portion of the left ventricle. The patient was apparently making a slow recovery, when he died suddenly three weeks following admission. It so happened that two hours prior to death the area of pulsation had been mapped out carefully (figure 1), and after death a needle was perpendicularly introduced through the center of the former observed area of pulsations until it penetrated to the anterior heart wall. After removal of the anterior chest wall a drawing was made in situ (figure 3). It could be seen that the left ventricle bulged ventrally and participated much more in the formation of the anterior heart wall than is usually the case. The area of the propulsion, which had been observed on the chest wall during life, was marked on the drawing with a broken line, and it was noted that it fell entirely within the aneurysmal bulge. The point where the needle penetrated was visible just within the left ventricular margin; the apical portion was exclusively formed by the left ventricle and revealed a globular bulge the size of a fist. The wall of the left ventricle measured 1½ cm. at the level of the coronary sulcus; corresponding to the bulge, it measured only 2 mm. in thickness and consisted mainly of scar tissue. This bulge and thinning out affected a great part of the ventral and dorsal wall of the left ventricle as well as the lower portion of the interventricular septum. The inner contour of the aneurysm was coated with shallow thrombi partly organized. The microscopic examination showed the aneurysmal wall to consist of scar tissue in which it was impossible to distinguish any muscle tissue.

It has therefore been demonstrated that the pulsation of the chest wall, as observed during life, coincided with the aneurysmal pouch, which had been forced ventrad and laterad by the systolic increase in the intraventricular pressure.

Case 2. G. F., male, aged 42. At the age of 36 this patient had experienced typical anginal pain on effort, radiating to the throat and into both arms, which came on only after exertion and ceased upon rest. Two years later there was considerable aggravation, the attacks of pain occurring more often and also during complete rest. One year later there were two very severe attacks of pain, each lasting for several hours. Then dyspnea developed, so that the patient was hardly able to climb one flight of stairs. He was admitted to the hospital on August 8, 1932.

Clinical findings: A forceful cardiac thrust was felt, both with the patient standing and lying down. The systolic propulsion could be palpated between the lower margin of the fourth and the sixth ribs. It was about 6 cm. broad and extended from the left midclavicular line almost to the left parasternal line with a maximum in the fifth interspace in the left midclavicular line. The heart sounds were of very low intensity; murmurs were not present. The second sound was heard everywhere better than the first. The heart rate was 86 per minute, and the rhythm was regular. The blood pressure readings during the four years of observation varied between 150/80 and 85/60. Electrocardiographic findings: A deep Q deflection in Leads I and II was noted, and in Lead I, T was negative with the R–T segment slightly depressed. A precordial lead was not available at that time. Radiological examination: The heart was moderately enlarged; the oblique diameter measured 14.4 cm. The apical portion was plump. No abnormal intersection was noted along the silhouette contour. The right lower cardiac border was revealed as having an increased convexity. Normal findings were noted along the aorta. The amplitude of pulsations was normal at the base and very small near the apical pole. The circumference of the palpable area of pulsation was outlined by lead marks and fluoroscopy showed that the lower border of the pulsation was adjacent to the apical portion. The center of the pulsation was

approximately 3 cm. above the apex region while the uppermost limit of the pulsating area was nearly 7 cm. distant from the apical portion.

The rest of the clinical examination was essentially negative. The urine revealed nothing abnormal, and the Wassermann reaction was negative. The patient improved, but steadily complained of effort-dyspnea and anginal pain. However, he was capable of working almost all the time as a cook. The blood pressure was low, with a systolic pressure usually below 100 mm. Hg. There was no change in the intensity and in the extension of the chest wall pulsations. Small amounts of digitalis and vasodilating drugs were beneficial. Four years later the patient died suddenly. On the basis of the peculiar precordial pulsation our diagnosis was cardiac aneurysm subsequent to coronary thrombosis affecting the ventral wall and apical portion of the left ventricle.

Postmortem findings: Over a localized area the pericardium was adherent to the ventral wall of the left ventricle. The heart was enlarged, the myocardium was grayish-red and pale in the inner layers. Over the lower anterior portion of the left ventricle, including the adjacent portions of the interventricular septum, there was a circumscribed saccular bulge, the wall of which showed extensive fibrosis and many grayish-whitish fibrotic areas on section. Both coronary arteries revealed a stenosing calcareous degeneration, and their lumen was almost occluded. The valves were normal.

In the next two cases to be reported the diagnosis of cardiac aneurysm was made on the basis of the characteristic palpable pulsation and was confirmed by radiological study.

Case 3. L. K., male, aged 68. This patient's condition started out in May 1933 with anginal pain which radiated into the left shoulder. Seven months later he had a very severe attack of pain in the cardiac area, with radiation into the left arm, lasting for 24 hours. He stayed in bed for two days only and then resumed his activities. Eight days later he experienced an even more severe attack, which was followed by unconsciousness. Fever developed and the patient stayed in bed for three months. A few months later, in April 1934, he came under our observation.

Clinical findings: With the patient standing one could notice a powerful systolic cardiac thrust with its maximum in the fifth intercostal space 4 cm. lateral to the left midclavicular line. The pulsation extended 3 cm. medial to the left midclavicular line. It could be palpated between the fourth and sixth ribs and was less distinct in dorsal decubitus. The apical sounds were of low intensity and hardly audible over the base. The heart rate was 52, and the rhythm was regular. The blood pressure was 115/65. Electrocardiographic findings: During four years of observation frequent alternation of sinus rhythm and middle nodal rhythm was noted. There were persistently present signs of cardiac infarction, namely, a deep Q and an inverted T in Leads II and III. With the exception of a moderate degree of pulmonary emphysema the rest of the examination was negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative.

The findings as to the chest wall pulsations, in connection with the history, caused us to diagnose cardiac aneurysm. The radiological study corroborated the clinical diagnosis. The roentgenogram (figure 4) revealed a bulge protruding at the middle of the left cardiac border. This was particularly well noted during fluoroscopy with the patient slightly turned into the left anterior oblique position, and this because of the extension of the aneurysm dorsad. The following observations as to the pulsations were made during fluoroscopy and indicated on the orthodiagraphic drawing (figure 5). During diastole the left ventricular contour appeared to be nearly normal; during systole, however, a bizarre shape appeared; the lower half of the contour revealed a normal inward movement while the upper half bulged outward. It was concluded that the lower portion of the ventricular wall had still sufficient muscular tissue

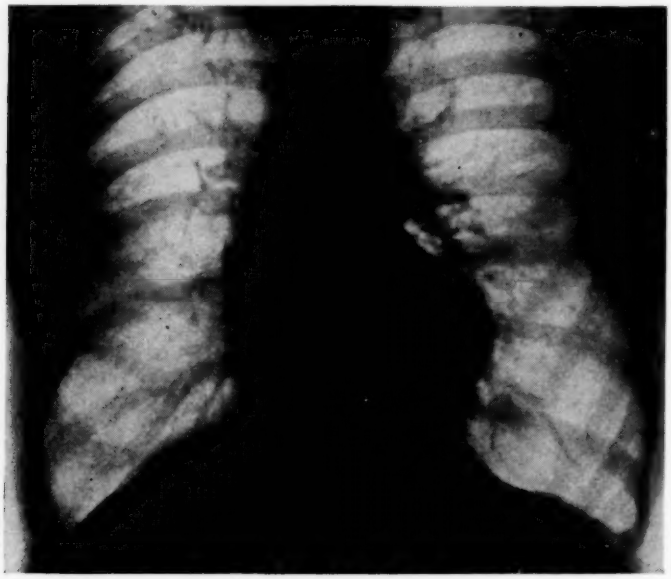

FIG. 4. Case 3. Roentgenogram: Anterior view showing a bulge along the left cardiac border.

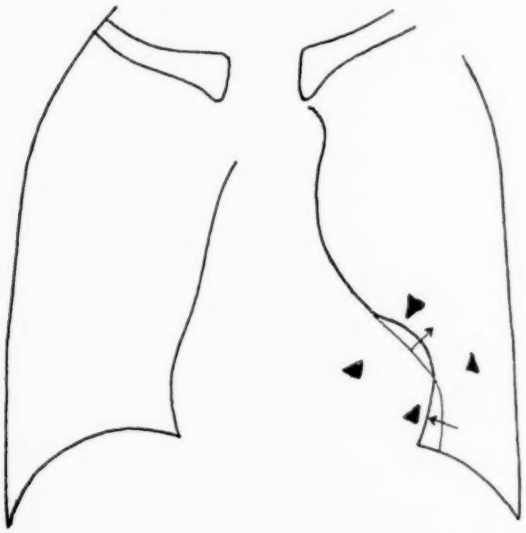

FIG. 5. Case 3. Orthodiagram showing the changes in shape along the left ventricular contour during systole, as indicated by arrows. The caudal part moves inward during systole, and simultaneously the cranial part is diverted outwardly. The limits of the area of the palpable precordial pulsation are indicated by lead marks. (This orthodiagram was made in expiration, whereas the roentgenogram (figure 4) was taken in deep inspiration.)

left to contract normally, resulting in a normal centripetal systolic movement, while the superior portion was attenuated and almost wholly transformed into scar tissue, so that it was forced outward by the high systolic intraventricular pressure. As an additional study the region of the palpable pulsation on the chest was marked by means of lead marks. The subsequent fluoroscopic examination showed (figure 5) the area of pulsation to correspond almost exactly to the upper ventricular portion. A roentgenogram taken in right anterior oblique view showed the barium filled esophagus to deviate slightly dorsad at the level of its lower third.

This patient has been observed over a period of four years, and he has been able to walk for half an hour at a time without distress. Ascending one flight of stairs, however, causes some dyspnea and chest pain. It is worth reporting that one year and a half after the coronary occlusion a gastrectomy was performed on this patient without any untoward cardiac complications.

Case 4. S. S., male, aged 46. At the age of 39, while watching a football match, he suddenly experienced severe oppression in his chest, lost consciousness and was brought to a hospital. Here a diagnosis of sunstroke was made, and the patient was discharged three days later on his request. He continued to work for eight days, but felt very ill and had another attack of unconsciousness; he was sent to a hospital again, where he stayed for 17 days. Because of cough he was rehospitalized two weeks later, on which occasion a diagnosis of cardiac aneurysm was made. Subsequently the patient felt all right and was able to walk for one hour straight without complaints. Carrying loads, however, would bring on pressure in his chest. Four years after the first attack the patient suffered another attack of severe anginal pain. A year later he came under our observation.

Clinical findings: There was present a very forceful, broad and resistant cardiac thrust distinctly felt in the fifth intercostal space and extending 3.5 cm. to either side of the midclavicular line. The quality of the pulsation was quite similar to the thrust noted in the presence of left ventricular hypertrophy, and the impulse was so forceful that during systole the entire lower half of the chest shifted jerkily from right to left, with even those parts of the chest below the sixth rib showing some pulsatory movement. The heart sounds were of very low intensity. Murmurs were not present. The heart rate was 72 per minute, and the rhythm was regular. The blood pressure was 110/65. Electrocardiographic findings: Low voltage was present in the limb leads. In Lead I, Q was well marked, R small, and the R–T segment was slightly elevated; a rather deep S deflection was present on Leads II and III. In the chest lead the normal initial downward stroke was practically absent. The rest of the clinical examination was essentially negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative.

The diagnosis of cardiac aneurysm was established on the basis of the history and of the pulsatory chest wall movements.

Radiological examination: The roentgenogram (figure 6) showed a marked enlargement to the left with the oblique diameter measuring 17 cm. At the upper third of the left contour there was noted an abrupt directional change below which a globular bulge appeared. During fluoroscopy this latter area showed clearly a systolic distention, while the adjacent cranial portion of the ventricular contour revealed a normal inward movement. A roentgenogram made two years later showed that calcium deposits had developed along the bulging part of the silhouette. The radiologic findings indicated that the aneurysmal enlargement affected not only the apical region but extended far craniad, involving the ventral and lateral walls of the left ventricle. A film taken in the right anterior oblique view showed a very slight impression on the lower third of the barium-filled esophagus. The aneurysmal bulge could be visualized ventrally (figure 7). By mapping out the area of chest wall pulsation by means of lead marks, we were able to demonstrate during fluoroscopy that the area of palpable

pulsation corresponded exactly to the bulge visible along the margin of the left ventricle.

Since the second attack of anginal pain in 1934 the physical condition of the patient has been exceptionally good, as shown by the fact that he can walk at a quick pace for an hour at a time and has been walking up and down four flights of stairs from four to six times daily without any distress. Running upstairs, however, brings on precordial oppression.

Case 5. P. W., male, aged 45. In January 1932 the patient experienced while walking a constricting pain over the cardiac area, which lasted for a few minutes. A few days later he had a very severe attack of pain associated with perspiration, which lasted for 26 hours, radiating into both arms and necessitating injection with morphine. A febrile reaction followed. Subsequently the patient stayed in bed for 10 days only.

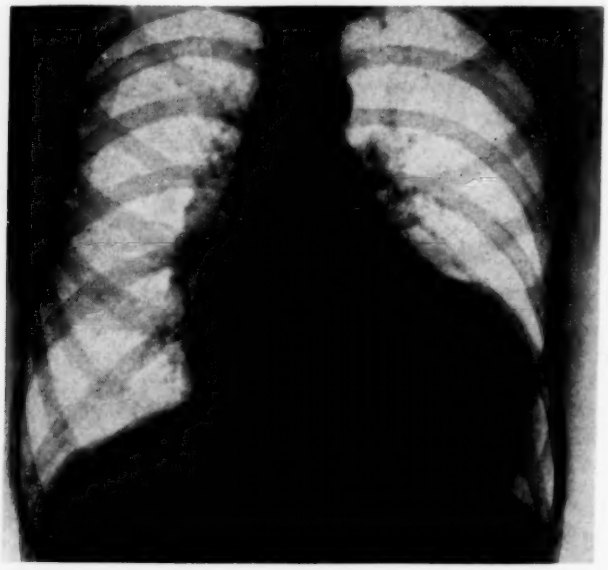

FIG. 6. Case 4. Roentgenogram, anterior view: The silhouette is considerably enlarged to the left, and along the upper ventricular contour a sudden change in direction is noted.

Clinical findings: Over a large precordial area a very forceful pulsation was noted, lifting not only the soft tissues but also the ribs. The maximum was at the level of the fifth rib, but the pulsation extended upward to the fourth, and downward to the sixth rib. This thrust reached unusually far medially—as far as to the left sternal border—and it was also felt 1 cm. outside the midclavicular line. It was most marked between the left parasternal and midclavicular line. The intensity of the heart sounds was low and there were no murmurs. The heart rate was 84, and the rhythm was regular. The blood pressure was 95/70. During the whole period of observation the systolic pressure never exceeded 115 mm. Hg. Electrocardiographic findings: Sinus rhythm, left axis deviation; a Q-wave was well developed in Leads I and II. In Lead I the R–T segment showed a minimal depression and T_1 was negative. In the chest lead the initial downward stroke was absent and T was inverted and very tall.

In view of the history and the electrocardiographic changes, both of which indicated coronary artery occlusion, it was felt that the forceful precordial pulsation should be interpreted as indicating an aneurysm affecting the ventral wall and apical portion of the left ventricle. From the particular location of the pulsation it was con-

cluded that the aneurysmal bulge affected the medial portion of the anterior wall of the left ventricle rather than the lateral portions. Radiologic examination: It was not surprising to find that there was no characteristic change along the cardiac silhouette, indicating a ventricular aneurysm. There was noted a moderate enlargement of both sides; the oblique diameter measured slightly less than 14 cm. There was no undue bulge along the cardiac contour, no sign of left ventricular hypertrophy. Fluoroscopy

FIG. 7. Case 4. Roentgenogram, right anterior oblique view: High degree of rotation. The aneurysmal bulge is noted ventrally.

revealed a normal systolic inward movement along the left ventricular margin, and it was therefore assumed that a sufficient amount of active muscular tissue was still present. The rest of the clinical examination was negative. Examination of the urine revealed nothing abnormal, and the Wassermann reaction was negative.

This patient was capable of a remarkable degree of physical capacity in spite of serious heart disease. While walking he seldom experienced precordial oppression. He was, however, often disturbed by a sensation of forceful pulsation in the cardiac

area, particularly while leaning against a desk. In the years following the first attack of pain he had practiced skiing, and he was able to climb to an altitude of 6,000 feet without any real discomfort and could hike for 10 hours a day. Six years following the coronary artery occlusion his physical condition was quite satisfactory and he was able to undergo considerable exertion.

The next case is the only one in the series in which a diagnosis of cardiac aneurysm was made exclusively on the basis of radiological findings.

Case 6. H. C., male, aged 60. This patient had had two severe and prolonged attacks of anginal pain. In October 1929 he was seized by a severe attack of pain of retrosternal location, and this was accompanied by much perspiration. The patient was kept in bed for four weeks and then resumed light work, but on walking he experienced chest pain. An orthodiagram was taken at that time and showed a moderate degree of enlargement to the left, but no changes indicative of cardiac aneurysm. Another attack of chest pain very severe in nature occurred three and a half years later. This pain lasted throughout the night and required three hypodermic injections. At this time the patient stayed in bed for five days. He never has had similar attacks of pain since. Three months later, in 1933, the patient came under our observation.

Clinical findings: It required the most meticulous examination in order to detect pulsatory phenomena over the cardiac area. There was one pulsation in the left anterior axillary line at the level of the sixth intercostal space that was moderately strong in character and confined to an area 3 cm. in width. In addition one observed a rather weak and diffuse pulsation in an area between the sternum and the left parasternal line, covering the fourth and fifth interspaces. The apical sounds were of low intensity and almost inaudible over the base. The heart rate was 90, and the rhythm was regular. Blood pressure was 105/60, and during the course of the next four years arose to 150/90. The chest of the patient showed a considerable degree of emphysema, kyphosis, and a depression of the lower portion of the sternum. The rest of the examination revealed nothing of particular significance. Nothing abnormal was found in the urine, and the Wassermann reaction was negative. Electrocardiographic findings: A deep Q-wave was present in Leads II and III; a negative T deflection in all conventional leads. It was, therefore, probable that in addition to the posterior site the anterior heart wall had shared in the infarction.

Radiological examination: The roentgenogram (figure 8) showed the whole heart enlarged, more to the left but also to the right. The left ventricular contour revealed a large half-spherical bulge, which took off from the upper portion of the ventricle at a sharp angle. When the patient was turned slightly into the left anterior oblique view, the bulge was observed to extend dorsad, while in the left lateral view the bulge appeared as a nuclear dense shadow within the cardiac silhouette. Examination of the barium-filled esophagus revealed an impression from in front at the level of its lower third. This impression coincided with the top portion of the aneurysm, but obviously was not caused directly by this aneurysm, for it was not this but rather the left atrium which must have been adjacent to the esophagus. In the right anterior oblique view this esophageal impression and deviation could be clearly demonstrated, but the nuclear shadow caused by the aneurysm was less distinctly visualized in this view. Fluoroscopy showed a systolic lateral pulsation along the aneurysmal bulge, particularly along its upper portion, while the adjoining part of the uppermost left ventricular margin revealed the normal inward movement.

Subsequent to the second attack of coronary occlusion, the patient was invalided for several weeks. He then gradually recovered and was able to walk slowly for from two to three hours without distress. Chest pain was experienced only when walking rapidly. Later he was knocked down by a bicycle and suffered a fracture of the skull and cerebral contusion. From that time greater distress was experienced.

Chest pain occurred even during rest, and at times Cheyne-Stokes breathing was present.

Case 7. R. R., male, aged 53. Without preceding anginal pain he experienced in November 1936 "heart burn" in the middle of the chest, lasting for a couple of hours without any radiation. According to his account, the discomfort had been only slight, but this statement was perhaps not reliable because it was learned that morphine had been injected for relief. The patient was kept in bed for eight weeks. The pain did not recur, and the patient complained bitterly that he was urged to avoid any

FIG. 8. Case 6. Roentgenogram, anterior view: The silhouette is enlarged to the right and to a greater degree to the left. Note how the left upper cardiac contour changes suddenly in direction where it meets the outline of the bulge.

physical effort in spite of his feeling perfectly well. He was first examined by one of us five months following the attack.

Clinical findings: A forceful systolic thrust was noted in the fourth and fifth intercostal spaces, particularly at the level of the fifth rib and extending from the left parasternal line to a point some 2.5 cm. beyond the midclavicular line. This pulsation could be felt better with the patient standing. The heart sounds were distant, just audible over the apical area but almost inaudible over the base. The heart rate was 84 and the rhythm was regular. Blood pressure was 110/80. The rest of the examination was entirely negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative. Electrocardiographic findings: In Lead I a Q wave was present, and the voltage of R was small. There was a deep S deflection in

Leads II and III. The initial downward stroke in the chest lead was absent. R–T segment in Lead I was slightly elevated, and T was negative. In Leads II and III, T was positive. In the chest lead the R–T segment was lowered and T positive.

On the basis of the abnormal pulsations, together with the patient's history and electrocardiographic alterations, a diagnosis of cardiac aneurysm was established. Radiologic examination (figure 9): The heart was distinctly enlarged to the left, and at about the middle of the left contour there was clearly noted a half-spherical bulge, which did not reveal an abnormal pulsation.

FIG. 9. Case 7. Roentgenogram, anterior view. The cardiac shadow is enlarged to the left and a half-spherical bulge is noted at the middle of the left ventricular contour.

Case 8. T. M., male, aged 59. In September 1934 the patient experienced a slight pain in the center of the chest, which responded to analgesic medication. One week later an attack of severe pain was experienced radiating into the left arm and lasting, with short remissions, for a period of three days. The patient was kept in bed for six weeks. From that time increased sensitivity to cold was noted, causing an unpleasant sensation in the cardiac area. A few months later there occurred severe attacks of cardiac asthma and pulmonary edema. At this time the patient came under our observation.

Clinical findings: Over a wide precordial area a pulsation was felt which forcefully lifted the soft tissues and ribs during systole. It was most marked in the fifth interspace in the midclavicular line, affecting also the fifth and sixth ribs. Laterally the thrust extended 2 cm. beyond the left midclavicular line, and medially it reached the left parasternal line, its total width measuring 9.5 cm. The character of the pulsation was hardly different from the one observed in the presence of left ventricular hypertrophy. The heart sounds were dull and of low intensity. Heart rate was 76; and the rhythm was regular. Blood pressure was 120/65. The rest of the examination was essentially negative. Nothing abnormal was found in the urine; the Wassermann reaction was negative. Electrocardiographic findings: A well marked Q deflection was noted in Lead I, and *a deep S* in Leads II and III, while in the chest lead the initial downward stroke was absent. The R–T segment in Lead I was slightly elevated, and T was negative. The S–T segment in Leads II and III was isoelectric,

and T positive. The S–T segment in the chest lead was much lowered, and T was isoelectric.

The referring physician reported that prior to the attack of pain there had been no elevation of the blood pressure.

The findings of abnormal pulsations in the precordial area, together with the history and the electrocardiographic alterations, indicative of cardiac infarction, led to the diagnosis of cardiac aneurysm affecting the ventral wall and apical portion of the left ventricle.

Radiologic examination: The cardiac silhouette was enlarged, particularly to the left, the oblique diameter measuring 17 cm. No abnormal bulge was noted. The area of the palpable cardiac thrust was indicated by lead marks, and subsequent fluoroscopy revealed the amplitude of pulsations at this level quite small. A follow-up study three years after the attack of pain revealed that the patient experienced slight dyspnea, but was well otherwise. He was being kept on small amounts of digitalis.

Case 9. P. R., male, aged 44. In April 1934 the patient experienced a very severe chest pain lasting for 24 hours. The cause was not recognized by the attending physician, and the patient was advised to use wet applications. In spite of the fact that he had fever he still tried to work but felt very weak and dizzy, and two weeks after the onset of the disease finally entered the hospital, where he remained six weeks. Since then anginal pain has made its appearance on rapid walking but never while at rest or when walking slowly. Ten months after the onset of the condition the patient came under our observation.

Clinical findings: A forceful pulsation was noted at the level of the fourth and fifth ribs, extending 2 cm. beyond the left midclavicular line and medially to the left parasternal line. The total width of the pulsation measured 9.5 cm. It extended upward to the third, and downward to the fifth interspace. The heart sounds were of low intensity. Murmurs were not heard. The heart rate was 72 per minute, and the rhythm was regular. Blood pressure was 135/65. Electrocardiographic findings: A deep Q-wave was present in Lead I, the initial downward deflection was absent in the chest lead. The R–T segment was isoelectric in the limb leads, while the S–T segment was depressed in the chest lead. T in Leads I and II was negative, in Lead III and in the chest lead positive.

Considering the history, the electrocardiographic findings, and the absence of hypertension in the past, the forceful precordial pulsation was interpreted as evidence of aneurysm of the anterior wall of the left ventricle.

Radiologic examination: The cardiac silhouette was considerably enlarged with an oblique diameter of 17 cm. The diaphragm was high in position. No abnormal bulge was noted. The area of the palpable cardiac thrust was mapped out by lead marks, and subsequent fluoroscopy revealed that the amplitude of pulsations over this area was very small, while the adjacent portions of the left ventricular border, particularly its basal portions, revealed a normal systolic inward movement.

A follow-up study three and a half years after the first attack of pain showed the patient satisfied with the condition of his health. He was capable of working as a tailor and also could do garden work. On walking rapidly, however, retrosternal pressure made its appearance.

Occasionally one has the opportunity to observe the development of both the palpable precordial pulsation and the bulge of the cardiac silhouette within a short time interval following the onset of anginal pain. This gives valuable aid in diagnosis.

Case 10. M. F., male, aged 56. This patient had been feeling well and did mountain climbing until the summer of 1935. A few months later he complained of an occasional jerking in the cardiac region, and often felt a drawing pain in the

right arm, lasting for two to three minutes. In December 1935 the patient experienced an attack of severe pain, starting in the right arm and spreading to the central portion of the chest and to the left arm, accompanied by perspiration. This lasted from noon until evening, but a chest pain of lesser severity was felt for several days longer. There was also a slight rise in temperature. The patient was in bed 10 days and then resumed work. He was seen on the twelfth day following the attack. Examination of the patient while standing revealed a barely palpable "apical thrust" in the fourth interspace in the left midclavicular line; high position of the diaphragm was also noted. The heart sounds were of low intensity and clear. Blood pressure was 125/90. Strict bed-rest was ordered. Reëxamination four weeks later revealed a large forceful pulsation corresponding to the place of the former "apical thrust." This propulsion extended from the third interspace to the fifth rib and its width was 7.5 cm. The larger part of the pulsation, 5 cm. in width, was outside of the midclavicular line. The smaller part, 2.5 cm. in width, was inside. The maximum of pulsation was in the

FIG. 10. Case 10. Roentgenogram, anterior view. The heart is considerably enlarged to the left, and the left lower portion of the silhouette bulges. Note the kinking at the cranial aspect of the left ventricular contour.

fourth interspace outside of the midclavicular line. Upon palpation of the propulsion, the patient stated that he felt "a tension" over this area and much more so when standing as compared with lying down. Electrocardiographic findings: Low voltage was present in all leads. The initial deflection in Lead I showed a deep Q, and the initial downstroke in the chest lead was absent. The R–T segment in Lead I was slightly elevated, and T was deep negative. In Lead III the T-wave was abnormally tall. The S–T segment in the chest lead was depressed, and T was positive.

Radiologic examination: On the occasion of the first examination, which was 12 days after the onset of the attack of severe pain, the heart was found to be in transverse position, moderately enlarged to the left, with an oblique diameter of 14 cm. Upon reëxamination six weeks later the heart was much larger and the oblique diameter measured 17 cm. (figure 10). The left ventricular contour revealed a large half-spherical bulge which took off near the base in the form of an angular kink. Along the bulge one could note during fluoroscopy a systolic lateral movement of small amplitude. In the right anterior oblique view the barium-filled esophagus was

noted to show impression from in front and to deviate slightly dorsad. The rest of the clinical examination was negative. Examination of the urine showed nothing abnormal. Wassermann reaction was negative.

Reëxamination one year and nine months later showed the left nipple corresponding to the area of precordial pulsation quite prominent and approximately 1 cm. higher than the right nipple. The good effort capacity of the patient nearly two years following the cardiac infarction was quite remarkable. The patient was able to walk for one hour and a half at a good speed without stopping, and also could climb two flights of stairs without discomfort.

Discussion

Our observations together with the experience of other writers, indicate that cardiac aneurysm can be diagnosed in many cases during life. To be sure, many of the symptoms and signs to which the earlier writers refer, have proved to be of no value for diagnosis. Thus, for example, the often cited systolic and diastolic murmurs were not noted in any of our cases, although particular attention was paid to this point; nor have we ever heard a gallop rhythm. The attempt to percuss out a cardiac aneurysm, as has been tried by earlier investigators, need not be considered seriously. In some cases we have found a sign not described heretofore. Corresponding to the location of the aneurysm, there was noted a bulge of the precordial region, associated with a slight upward displacement of the left nipple. In not a few cases there was present a steady sensation of precordial pain; sometimes it could be elicited by pressure applied to a limited area of the chest, the area coinciding on the whole with the summit of the pulsating region of the wall of the chest. Yet this symptom, which Lutembacher [2] considered to be of diagnostic importance, was too ambiguous to be a dependable basis for the recognition of cardiac aneurysm.

Of all the diagnostic findings mentioned in the older literature of the subject, pulsations in the cardiac area have proved to be of greatest value. In nine of the ten cases which have been the subject of this inquiry, we were able to make the diagnosis of cardiac aneurysm primarily on the basis of a pulsatory finding. In only one case was the radiological examination of decisive value for the diagnosis. The precordial pulsation is the most frequent sign of cardiac aneurysm. The force and extent of this pulsation must naturally vary from patient to patient, depending upon the size of the aneurysm, the amount of thrombotic material lining the aneurysmal wall, the extent to which lung tissue intervenes between the cardiac and thoracic walls, and, finally, upon the thickness of the tissues overlying the bony chest wall. It will, therefore, be readily understood that pulsations of the chest wall are absent not only in cases of aneurysms affecting the posterior wall of the heart, but that in certain circumstances they may be missed even in those cases in which the aneurysmal bulge is located on the anterior wall of the heart.

The localization of the pulsation naturally depends upon the location of the aneurysm and upon the position of the diaphragm. In the great ma-

jority of cases we found the maximum pulsaition at the level of the fifth rib, in the neighborhood of the left midclavicular line. The characteristic pulsation is not of that circumscribed type which is often present in cases of hypertrophy of the left ventricle, but is rather a diffuse, large cardiac thrust; it extends not only over several intercostal spaces but is remarkable for its width, which often measures from 7 to 9 cm. In cases where the radiological examination reveals a bulge along the left ventricular margin, the pulsation may extend considerably beyond the left midclavicular line. Sometimes, however, the maximum pulsation is found inside the midclavicular line, and extends considerably medially. This is found in cases where the aneurysmatic distention apparently affects the parts of the anterior ventricular wall near the septum and where the radiogram reveals but little widening of the left ventricular margin.

The palpable pulsation is generally quite forceful and its resistance is certainly not less than that of the powerful pulsation caused by a hypertrophic left ventricle. Sometimes it is actually not possible to distinguish clearly between hypertrophy of the left ventricle and cardiac aneurysm. It is rather the diffuse character of the cardiac thrust, its localization above the fifth intercostal space, and its considerable extent towards the sternum that are indications of the existence of a cardiac aneurysm. In each case it is recommended that all those factors be excluded which might be causative of left ventricular hypertrophy. The history and electrocardiographic findings of preceding cardiac infarction are valuable supporting evidence. Sometimes one is able to watch the development of a precordial pulsation following coronary artery occlusion, and this supports the diagnosis. The pulsation may be noted within a few days following the attack of pain, and quickly develops its permanent character. If once established, no further changes in the pulsatory phenomena due to cardiac aneurysm were noted in our cases during the subsequent years. Occasionally a pulsation may undergo regression a few weeks after its appearance.[17]

If the radiological examination reveals characteristic alterations, these are without doubt the most definite and trustworthy signs of a cardiac aneurysm. There may be a circumscribed bulge along the margin of the left ventricle, usually at the level of the middle or upper portion of the left cardiac contour and an abrupt change in the course of the left cardiac margin, as a rule seen near the base. One can often recognize the aneurysmal nature of a bulge by a systolic lateral pulsation, which contrasts sharply with the normally directed centripetal movement of the adjacent, intact muscular portions of the ventricle. Obviously we must not confine ourselves to the study of the roentgenogram, but must also subject the patient to a very careful fluoroscopic examination; it is then not unusual to find a very slight bulge which was not noted in the roentgenogram, while the observation of a systolic lateral pulsation proves the existence of a cardiac aneurysm at this level. For the proper timing of such pulsations it suffices to compare the pulsation observed with the radial pulse. Occasionally the bulge in the anterior wall

of the left ventricle is best visible with the patient in the right oblique anterior position. Calcium deposits in the wall of the aneurysm were observed only once in our series.

Wolferth, Wood and Bellet [18] reported a case of a large aneurysm of the posterior wall in which the difficult passage of barium through the lower third of the esophagus attracted attention. In five of the seven cases which we examined especially with this in mind, we were able to observe in the right anterior oblique view at the lower third of the esophagus a slight impression from in front and a dorsal displacement at this level. These cases had shown no signs of cardiac failure. We were not able to decide whether these changes in the esophagus were caused by a dilation of the left atrium, as a result of inclusion in the process of infarction; or whether they were due to a backward displacement of the left ventricle, whose anterior portion was the seat of the aneurysm, as has been suggested by other observers.[8, 22]

The radiological examination revealed in seven cases definite enlargement to the right, and this in patients who had never shown signs of cardiac insufficiency. Similar changes were noted in two cases of cardiac aneurysm in another series of topographical anatomical studies, on which we shall report in detail later. In those cases a very considerable distention of the anterior wall of the left ventricle, chiefly towards the right, was observed, which resulted in a shifting of the anterior longitudinal sulcus towards the sternum. Associated with this was a displacement of the right ventricle; its right contour, which normally coincides with the right margin of the sternum, was displaced far laterad.

In one half of our cases the radiological study revealed no characteristic changes. Yet the percentage of cardiac aneurysm without pathognomonic radiological changes is obviously higher, for in this study we have included only those cases where there was no doubt as to the diagnosis, and a considerable number of cases escape clinical diagnosis and are discovered only at autopsy. In such cases the radiological examination reveals only an enlargement of the apical region which has no special characteristics.[19] Often a small pulsatory amplitude along the left ventricular margin has been noted. Many authors [2, 12, 19] have remarked on the rarity of characteristic radiologic findings. In order to understand this fact it should be remembered that not all cases of cardiac aneurysm reveal a bulge along the surface of the heart. Often they merely form shallow pittings on the inner surface of the ventricle, which are only perceptible upon inspection of the interior of the heart.[20] The resistance of the fibrous, attenuated ventricular wall may be considerably strengthened by thickening of the epicardium, by an adherent pericardium, and further, by the deposit of layers of thrombotic clot along the inner surface, so that both circumscribed bulge and abnormal pulsatory phenomena may be absent.[15] Moreover, among the cases of cardiac aneurysm with a bulge of the ventricular wall are only those accessible to radiological diagnosis, where the aneurysm is not confined to the apical

region. These cases are rather rare. By far the larger number of cases of cardiac aneurysm are situated in the apical area, and in the nearby regions of the anterior wall of the left ventricle, and of the septum. These aneurysms of apical location are buried in the left hepatic lobe, making for themselves a bed in this organ, and they appear by radiological examination as an uncharacteristic elongation of the apical portion of the left ventricle.[2]

The diagnosis of cardiac aneurysm is much enhanced by finding evidence of a preceding cardiac infarction. Hence, in addition to a good history, electrocardiographic alterations are of great significance. Actually, in none of our 10 cases were electrocardiographic signs for cardiac infarction missing; and this included instances of many years' duration. Eight cases revealed the characteristic features of the anterolateral location, while two showed evidence for postero-diaphragmatic site. The dorsal extension of the aneurysm in these two cases could be demonstrated by the radiological examination. In one of them, with a history of two attacks of pain, there was electrocardiographic evidence for both anterior and posterior location. In half of our cases there was noted a deep S deflection in Leads II and III, and this included cases where there were no findings indicative of left sided hypertrophy. The electrocardiographic changes once developed appeared to be very constant in our cases of cardiac aneurysm.

All of the cases which we have observed have occurred in males. This is not remarkable in view of the fact that sclerosis of the coronary arteries, without associated hypertension, shows a definite prevalence in the male sex. The age at which coronary artery occlusion occurred varied in our patients between 39 and 64 years. Four cases occurred in early middle-life (39, 39, 40, 43 years, respectively).

It is noteworthy that one half of our cases have suffered two or even three severe anginal attacks of long duration. In three cases the attack was accompanied by loss of consciousness. Mention should be made of the significant fact that out of our 10 cases, only two had had complete and prolonged bed rest. In the eight remaining cases rest in bed was limited to a few days only, for the simple reason that the nature of the disease was not recognized at that time. The knowledge of this fact should possibly prove of significance in an attempt to prevent the formation of a cardiac aneurysm. Adherence to the prescribed régime of strict and prolonged bed rest, however, will not provide absolute protection, as is demonstrated by one of our cases. This patient had adhered strictly to a régime of rest from the very beginning of the disease.

Our final remarks concern the prognosis of cardiac aneurysm, the question of the expectation of life and of physical capacity of those afflicted with the disease. We are well aware that the validity of the following conclusions is limited since our study has been based solely upon those cases which have been recognized during life and have been under our observation for periods up to four years; cases which were not discovered until autopsy were not taken into consideration. Out of our 10 cases, sudden

death occurred in two; in one three months and in the other four years after the onset of the coronary artery occlusion. Eight patients are still living, and in these the periods of survival following the occlusion are as follows: one, two, three, three and a half, four, four, six and seven years, respectively.

The capacity of these patients for physical effort is quite striking. When we learn that a patient with a large cardiac aneurysm is able to ascend the stairs to his fourth-story apartment at a normal speed without distress; that another has been the subject of a gastrectomy without any ensuing cardiac complications; and, finally, that still another is able, despite his cardiac aneurysm, to ski, to walk for 10 hours on end and to climb a mountain with an altitude of 6,000 feet, these facts give us a vivid impression of the astounding physical capacity of such hearts. Our observations agree with the experience of other authors,[5, 15, 17] who report upon satisfactory cardiac function in patients suffering from cardiac aneurysm. If the muscular structure of the heart as a whole is not seriously injured, it would appear that quite a considerable part may be out of function and that this condition is borne relatively well. Experience with cases in which rather extensive destruction of the heart muscle by malignant tumors has occurred is in agreement with this opinion.[21]

Summary

Ten cases are reported in which the diagnosis of cardiac aneurysm was made during life. In two of these cases the diagnosis was verified by postmortem examination, while in five cases characteristic radiologic findings were obtained.

The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the midclavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more craniad than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic valvular lesions, can be excluded. It is especially significant if the development of such a pulsation can be observed subsequent to a coronary artery occlusion.

In our material we have not observed murmurs nor any particular findings obtained by means of percussion.

The radiological examination revealed characteristic features only in half of our cases. This should be explained by the fact that the aneurysmal development is most often limited to the apical portion of the heart. This

location results merely in an elongation of the apical portion of the silhouette, such a finding being not characteristic in any way. Pathognomonic findings in the roentgenogram, however, may be expected for those cases where the aneurysmal formation involves the basal or middle portions of the left ventricle. One may then expect to find along a part of the left lower cardiac contour one or the other of the following findings: a localized bulge, a sudden kink, a centrifugal, systolic pulsation, calcification, shell-like in arrangement. The esophagus may reveal in its lower third either an impression from in front or a shallow deviation dorsad.

Electrocardiographic alterations indicating cardiac infarction were well marked in all of our cases and remained unchanged over a course of years. A deep S deflection in Leads II and III was strikingly noted in one half of the cases.

The prognostic outlook in the presence of cardiac aneurysm is relatively favorable. This refers both to expectation of life and to effort capacity.*

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* After completion of this article a paper of J. Parkinson, D. E. Bedford, and W. A. R. Thomson appeared (Quart. Jr. Med., 1938, vii, 455) dealing with cardiac aneurysm. The authors particularly stressed the importance of the radiological examination for the diagnosis of cardiac aneurysm and gave an excellent description of its radiological features. It seems to us that a thorough consideration of physical signs apart from roentgen-ray examination might considerably increase the number of diagnosed cases of cardiac aneurysm. Also a paper by Louis H. Zerk, Am. Heart Jr., 1939, xvii, 569–580, called attention to the cardiac aneurysm.

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STUDIES IN THE METABOLISM OF DEXTROSE FRAGMENTS IN MAN *

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Introduction

The problem of producing a substitute carbohydrate for dextrose in the treatment of diabetes has been studied extensively by various investigators. This subject was comprehensively reviewed by Gottschalk [1] in 1929. Not any of the compounds studied has proved satisfactory from the point of view of being metabolized with a smaller amount of insulin than is dextrose. Moreover these compounds have defects as to availability, toxicity and taste. Perhaps the most promising substance studied for this purpose was dihydroxyacetone, investigated by Rabinowitch.[2] The possible merits of this substance at present, at least, are off-set by the cost of manufacture and its comparative instability.

In 1907, Nef [3] showed that when dextrose was treated with diluted, strongly dissociated alkalies the molecule theoretically could form 116 different substances of which he was able to identify 93; 47 of these were sugars and the rest fragments of sugar cleavage. Later Fischler [4] showed that dextrose treated with dilute alkali produced quantities of methyl glyoxal.

It occurred to the authors to study the metabolism of this mixture of sugar fragments as an entity. Its possible use as a substitute carbohydrate in diabetes suggested itself.

Preparation of Alkalinized Dextrose

Alkalinized dextrose was prepared according to the method of Nef.[5] A cold solution of 100 grams of dextrose in 500 c.c. of water was shaken with 0.5 gram of calcium oxide and heated at 70° for an hour; then an additional 0.5 gram of calcium oxide was added and the temperature was maintained at 70° for another hour. This last operation was repeated. The dark red, neutral solution obtained was distilled under diminished pressure to remove water until 100 c.c. of the syrupy solution remained. One cubic centimeter of this solution represents one gram of dextrose employed. The fate of dextrose submitted to this calcium hydroxide treatment was followed polariscopically. The reduction in optical activity was prompt and uniform in

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consecutive samples treated by the foregoing procedure. The dextrose reached a minimal specific rotatory power of $[\alpha]\frac{25°}{D} + 3.7$ after the complete treatment, as evinced by the fact that subjecting the same mixture to the process again did not effect any change in optical activity. Six months standing under laboratory conditions did not alter the rotation. Varying quantities of dextrose were added to a 5 per cent solution of alkalinized dextrose and the rotation was determined immediately. The addition of 5 per cent dextrose to alkalinized dextrose changed the rotation of $[\alpha]\frac{25°}{D} + 3.7$ to $[\alpha]\frac{25°}{D} + 7.7$; the addition of 1 per cent gave a value of $[\alpha]\frac{25°}{D} + 5.0$. Smaller quantities of unaltered dextrose could not be detected by this method.

The copper reducing power (Fehling's solution, Munson-Walker method) is quantitatively the same as dextrose. However, at 25° the quantities of cuprous oxide formed by alkalinized dextrose measured at 15 minute intervals over one hour were approximately three times greater than those produced by dextrose under the same conditions.

The heat of combustion per c.c. is 3.17 calories compared with 3.74 calories per gram for unaltered anhydrous dextrose.

Optical rotation studies, reduction tests and the constancy of caloric value in consecutive samples indicate that alkalinized dextrose is uniform in composition and the authors believe that there is no dextrose in the mixture that has not been altered by the alkali treatment.

Method of Study

Elsewhere[6] the authors have shown that in rats, dogs and rabbits dextrose treated in this manner is not toxic. Furthermore, the substance was shown to be capable of being utilized by the rat as evidenced by additional glycogen storage in the liver. However, the feeding of alkalinized dextrose by stomach tube did not significantly raise the respiratory quotient of the rat during 2½ hour periods, when measured by a modification of Haldane's open circuit apparatus.[7] In the rabbit alkalinized dextrose produced only a very mild hyperglycemia when administered by stomach tube (nine experiments) or by vein (22 experiments); a summary of these results is shown in charts 1 and 2.

These findings prompted experiments on normal and diabetic humans. Eight-tenths of a gram of dextrose and 0.8 c.c. of alkalinized dextrose respectively, per pound of body weight, were administered orally to previously fasted normal individuals allowing at least 48 hours to elapse between tests. The blood sugars were determined by the Folin[8] micro method. The results are set forth in table 1.

Another series of 12 normal individuals were given dextrose and alkalinized dextrose tolerance tests using the divided dose method. Twenty-

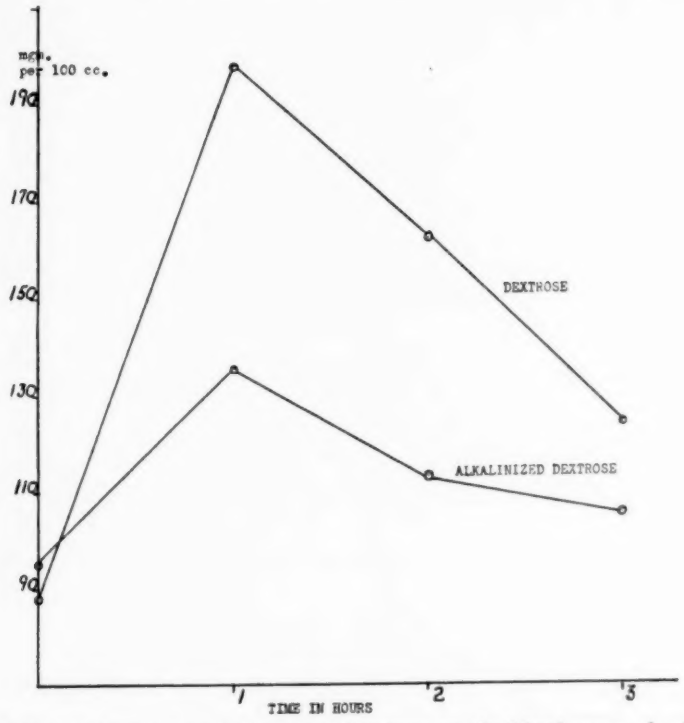

CHART I. Action of dextrose and alkalinized dextrose on the blood-sugar of rabbits orally.

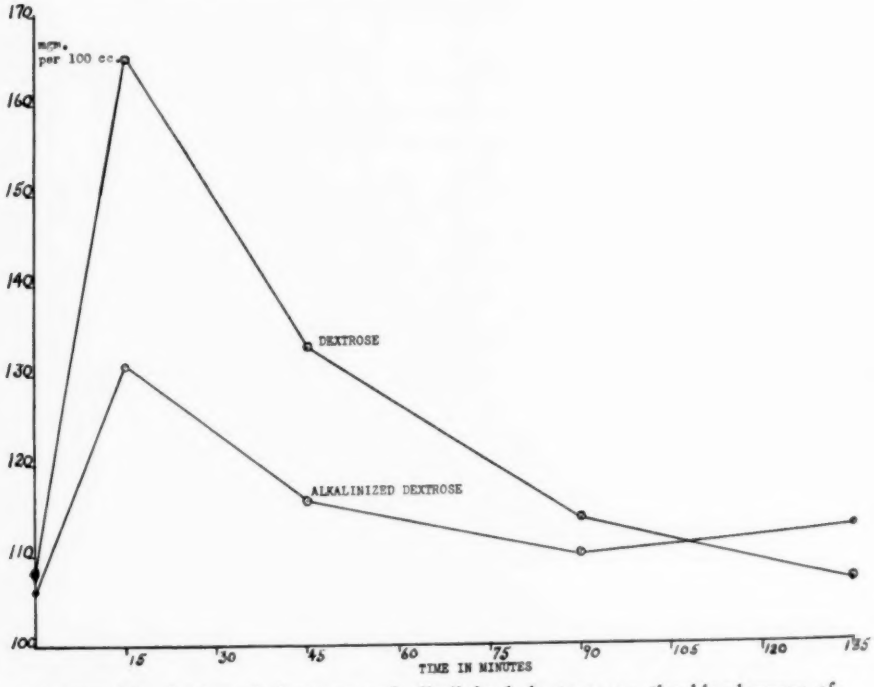

CHART II. Action of dextrose and alkalinized dextrose on the blood-sugar of rabbits intravenously.

TABLE I

Blood Sugar Curves in Man

Subject No.	Weight lbs.	Substance Administered	Mg. per 100 c.c. blood						Urinary sugar End of 1 hour
			Fasting	½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.	
1	216	Dextrose	59	164	183	182	194	166	+
		Alkalinized dextrose	103	162	190	151	141	139	++
2	104	Dextrose	91	183	179	165	159	129	++
		Alkalinized dextrose	100	151	192	132	129	119	+++
3	128	Dextrose	100	139	143	114	103	93	–
		Alkalinized dextrose	93	131	113	121	96	102	+
4	132	Dextrose	105	88	156	180	99	lost	lost
		Alkalinized dextrose	100	154	133	125	122	lost	–
5	126	Dextrose	87	185	163	111	87	lost	+
		Alkalinized dextrose	100	188	210	145	83	86	++++
6	167	Dextrose	101	97	96	98	96	98	–
		Alkalinized dextrose	93	110	92	91	87	90	+
7	145	Dextrose	108	123	156	143	120	lost	–
		Alkalinized dextrose	87	130	118	120	117	lost	–
8	113	Dextrose	96	196	194	134	133	117	+
		Alkalinized dextrose	99	183	156	105	108	94	+
9	152	Dextrose	100	183	169	126	96	90	+
		Alkalinized dextrose	98	143	165	130	122	100	++
10	165	Dextrose	85	166	121	116	98	77	–
		Alkalinized dextrose	97	143	115	128	104	96	++
11	162	Dextrose	91	140	143	112	98	88	–
		Alkalinized dextrose	94	170	112	100	108	95	+++
12	151	Dextrose	97	106	133	119	104	90	–
		Alkalinized dextrose	119	157	149	144	122	118	++++
13	130	Dextrose	96	123	131	102	94	100	–
		Alkalinized dextrose	99	171	160	165	134	96	++++
14	136	Dextrose	91	129	136	107	94	89	–
		Alkalinized dextrose	98	135	148	140	108	99	++++
15	150	Dextrose	93	155	170	124	118	96	–
		Alkalinized dextrose	105	164	120	170	112	105	++++
16	140	Dextrose	82	200	155	119	74	81	–
		Alkalinized dextrose	91	169	154	161	109	92	++++
17	167	Dextrose	105	178	133	122	110	95	–
		Alkalinized dextrose	105	152	118	146	129	126	++
18	155	Dextrose	93	119	164	115	89	86	+
		Alkalinized dextrose	94	156	137	154	121	95	++++
Average		Dextrose	93	150	151	127	109	99	
		Alkalinized dextrose	98	154	143	135	114	92	

five grams were given after fasting and 25 grams one half hour later. The average of these results is shown in chart 3.

A study of table 1 and of this average value indicates that the low blood-sugar curves observed when alkalinized dextrose was administered to rabbits did not obtain in normal man.

A series of 12 moderately severe diabetics were studied according to the divided-dose tolerance tests. These results are shown in chart 3.

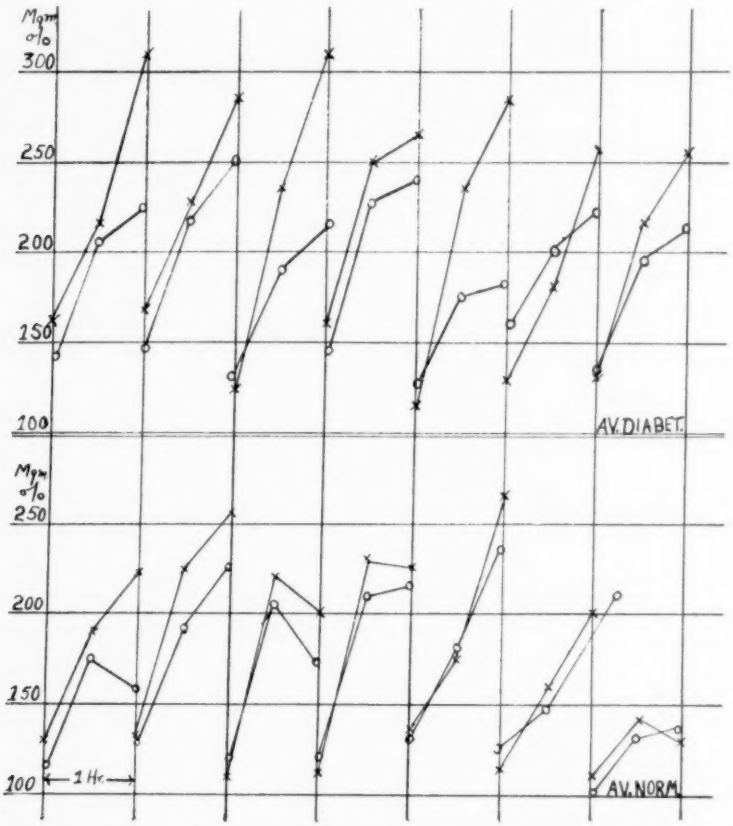

CHART III. Action of dextrose and alkalinized dextrose on the blood-sugar of diabetic subjects.

x Dextrose.
o Alkalinized Dextrose.

DISCUSSION OF RESULTS

The treatment of dextrose with strongly dissociated alkali solutions according to Nef [3] causes the hexose to undergo degradation into simpler molecules. The first effect of the hydroxyl ion is a likely rearrangement of the dextrose molecule into its β and γ forms. The more labile forms then produce alkali glucosate with the rupture of the oxide ring and finally undergo cleavage into three carbon-atom chains. Among the more common

products identified by Nef were methyl glyoxal, glyceric aldehyde, glyceric acid, trihydroxybutyric acid, tetrahydroxyvaleric acid and glycollic acid. The lowered oxygen consumption upon combustion indicates that partial oxidation has occurred. It was the thought of the authors that these sugar fragments might catabolize in the body directly (without conversion into glycogen) with a lesser amount of insulin or perhaps elicit the secretion of more insulin from the impaired islet tissue as Gottschalk [1] suggests is true of fructose and dihydroxyacetone.

Results of glycogen storage in the liver of the white rat showed definitely that there is no significant difference between glycogen storage as induced by the feeding of dextrose and that caused by the feeding of alkalinized dextrose. This indicates the capacity of alkalinized dextrose to form glycogen.

The inability of alkalinized dextrose to increase the respiratory quotient or the oxygen consumption of the rat indicates that the direct utilization of the mixture in the animal body is unlikely, and that its metabolism will occur only after previous conversion into glycogen. Kermack [9] et al. have shown that dihydroxyacetone may be directly utilized by the body tissues, yet Ringer [10] and Frankel have demonstrated that this triose is almost quantitatively converted into dextrose in the animal body.

Like dihydroxyacetone, alkalinized dextrose combats insulin shock in mice.

The curves for the blood-sugar levels of rabbits with dextrose and alkalinized dextrose are strikingly dissimilar. By oral and intravenous administration, the hyperglycemia produced by alkalinized dextrose was far less marked than that produced by dextrose. We attribute this to the rapid polymerization of the sugar fragments into glycogen thus causing a diminution of reducing substances in the blood.

In normal man, table 1 and chart 3 show that this condition does not obtain and that the hyperglycemia determined as dextrose produced by each substance is substantially the same. We are unable to offer any explanation for this difference in response to alkalinized dextrose between the rabbit and man unless the liver of the rabbit is better capable of polymerizing the fragments of the dextrose molecule than the liver of man. In this connection it is interesting to note that Grevenstuk and Laquer [11] observed that dihydroxyacetone given intraperitoneally to mice and rats was converted into glycogen, but when given orally to man the substance produced lactic acid which appeared in the blood and urine.

It is interesting to note that most of the individuals showed a transient glycosuria with alkalinized dextrose which, however, was not sufficient to account for the difference in blood sugar in diabetics, assuming the absorption to be the same as that of untreated dextrose. Perhaps some strongly reducing dextrose fragments in the urine were responsible for this observation.

In normal man the degrees of hyperglycemia with dextrose and alkalinized dextrose were practically the same. With smaller quantities of dextrose

and alkalinized dextrose in 12 moderately severe diabetics, the hyperglycemia with the latter in all instances was less than that produced when dextrose was ingested (chart 3). In diabetes, where possibly the utilization of dextrose is disturbed to a greater degree than the polymerization of this sugar, this substance seems to warrant further trial. On the basis that polymerization is necessary to the catabolism of alkalinized dextrose, the possibility of diminishing post-prandial hyperglycemia presents itself. Besides, the desirable taste and the inexpensiveness are factors of practical importance. The authors commend the further study of this substance as a substitute carbohydrate in diabetes in institutions where a large diabetic service is available.

Summary

The metabolism of alkalinized dextrose in animals, normal and diabetic man has been studied and compared with that of dextrose. Its possibility of use as a substitute carbohydrate in diabetes has been discussed.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH SULFAPYRIDINE *

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Several communications dealing with the clinical applications of sulfapyridine (2 sulfanyl-amino-pyridine) have appeared since Whitby's (1938) report of its value in the control of pneumococcic infections in mice. Among the first of these and one of great importance, is that of Evans and Gaisford (1938), which gave hope that a drug of value had been discovered. Subsequent work is confirming this belief.

The purpose of this communication is to describe our experience in the treatment of pneumococcic pneumonia in the Indianapolis City Hospital and in the private pavillion of the Methodist Hospital during the fall and winter of 1938–1939.

Methods

All patients with pneumococcic pneumonia were treated with sulfapyridine. The following procedures other than routine examinations were employed to verify the diagnosis and follow the course of the disease: sputum typing, blood cultures, blood counts, roentgenograms, occasional lung puncture and urea clearance tests. Determination of the amount of free sulfapyridine in the blood was made by a modification of the method of Schmidt (1938) in which the concentration of sodium β-naphthoquinone-4-sulfonate was increased from 0.2 per cent to 0.5 per cent. The color thus obtained follows Beer's law more closely than that given by the weaker reagent. The color intensity was measured with the Evelyn photoelectric colorimeter. We are indebted to Dr. O. M. Helmer of the Lilly Laboratory for Clinical Research, through whose courtesy these determinations were made.

Oxygen and other supportive measures were used wherever the clinical condition of the patient indicated the need. The patients were treated in the wards without special nursing care.

Dosage

The total amount of sulfapyridine given varied markedly from patient to patient but the dose during the first 36 hours was standardized. Treatment was begun with an initial dose of 2 gm. followed by 1 gm. at two or three hour intervals during the next 36 hours. This approximated a total dose of 1 grain per pound or 0.12 gm. per kg. during this period.

Further administration of the drug depended on: (1) the severity of toxic manifestations, i.e., vomiting, skin rash, mental confusion or depres-

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sion; (2) the rectal temperature at the end of 36 hours of treatment; (3) the concentration of free sulfapyridine in the blood; (4) change in the number of leukocytes. Vomiting occurred at some time during treatment in about 80 per cent of the patients. Bacteremia and extensive consolidation of the lungs were considered indications for giving the maximum amount of the drug which the patient could tolerate.

The largest dose (98 gm. in 11 days) was given in Case 5 (figure 1), a patient admitted on the seventh day of the disease with symptoms of virulent infection. On admission, 200,000 units of anti-pneumococcus rabbit serum were given because the supply of sulfapyridine was temporarily exhausted. The serum appeared ineffective and 24 hours later sulfapyridine was begun. Nine grams were given daily for five days. Although the bacteremia disappeared promptly, clinical improvement was slow. Seven grams were therefore given daily during the next six days. Neither leukopenia nor anemia occurred.

Results

An unselected group of 50 patients was treated with sulfapyridine during the fall and winter of 1938–1939. Recovery was surprisingly rapid when treatment was begun early. The fall of temperature and leukocytes

Table I

State of Patients Treated with Sulfapyridine

Type	No. of Cases	No. Cases over 40 yrs. Age	Duration more than 3 days	No. Lobes Consolidated			Bacteremia	Empyema or Effusion	Extension	Avg. Maximum Blood Conc. mg. 100 c.c.	Died
				1	2	3					
I	9	3	3	2	5	2	3	1 Empyema	0	8 mg.	0
III	6	5	0	4	2	0	0	1 Empyema 1 Effusion	1	6 mg.	0
IV	4	3	0	1	3	0	0	0	1	4 mg.	0
V	14	1	8	4	8	2	4	2 Effusion	1	6.5 mg.	1
VI	1	0	1	1	0	0	0	0	0	7.3 mg.	0
VII	6	2	5	2	4	0	0	1 Empyema	2	4.5 mg.	0
VIII	2	1	0	0	2	0	0	0	0	4.1 mg.	0
XII	1	0	0	1	0	0	0	0	0	3 mg.	0
XIV	3	2	3	1	1	1	1	0	1	16 mg.	2
XVIII	1	0	1	0	1	0	0	0	0	5.8 mg.	0
XIX	1	0	0	0	1	0	0	0	0	8 mg.	0
XXIII	1	0	1	0	1	0	0	0	0	6 mg.	0
XXIX	1	0	1	0	1	0	0	0	0	7 mg.	0
Total	50	17	23	16	29	5	8	3 Empyema 3 Effusion	6		3

was impressive (figure 1) with the pulse and respiration rate shortly following. The symptoms and signs of infection quickly left the patient and were replaced by a feeling of well being. This change of state was striking and might occur within 24 hours. One often saw a patient who on admis-

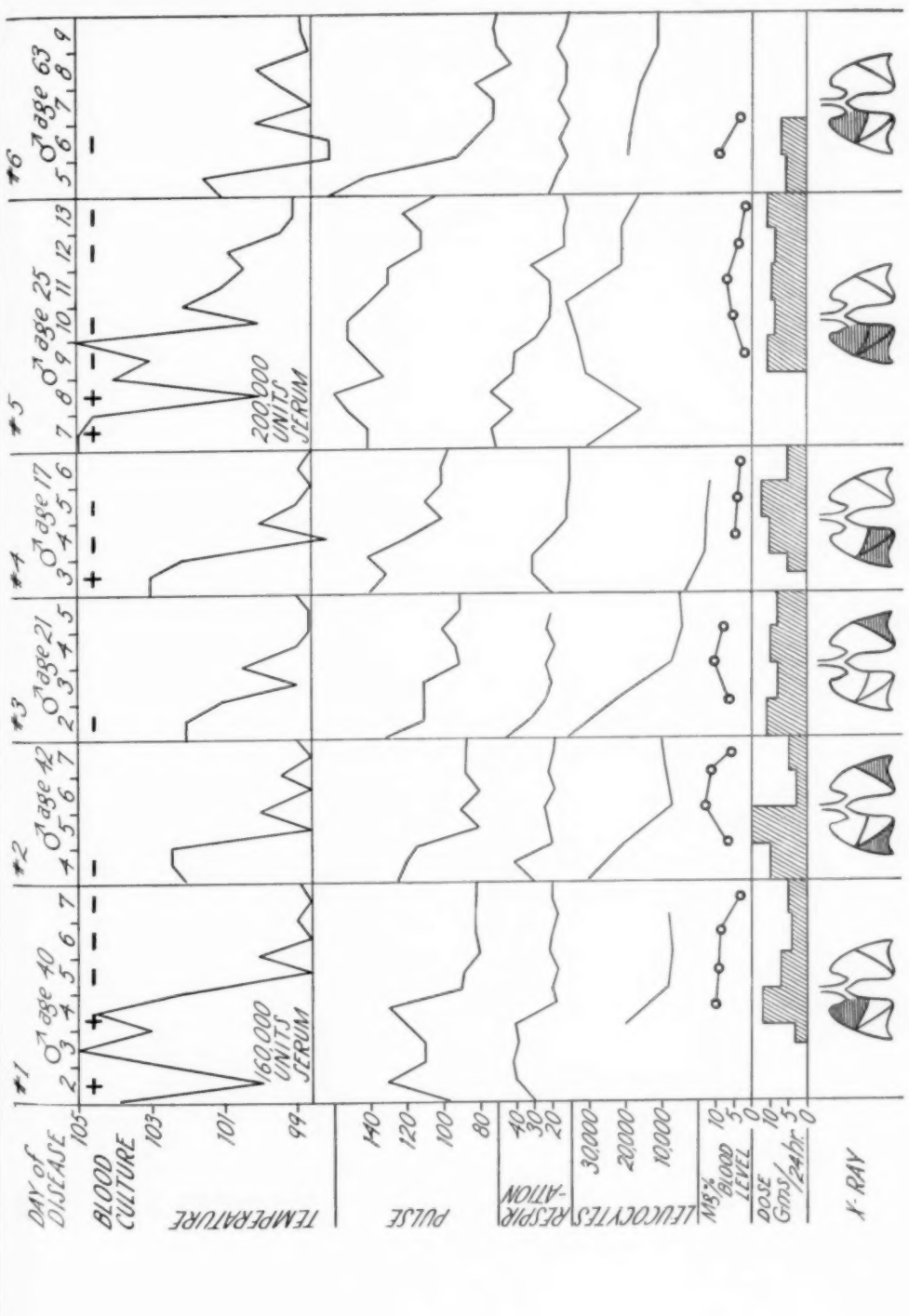

FIG. 1. Clinical summary of six patients with Type I infection.

sion was restless, sweating, apprehensive, and tachypneic, obviously desperately ill, change within 24 hours to one who appeared well. Crisis occurred in 41 patients within 36 hours after treatment was initiated. The fall in six patients was by lysis. It is important that the fever was not affected by the drug in two of the patients who died.

We have been unable to establish a direct relationship between dosage and concentration of free sulfapyridine in the blood. Large doses several times failed to raise the blood level to the high concentrations observed in other patients who received smaller amounts of the drug.

Eight patients recovered when the maximum blood concentration of free sulfapyridine averaged less than 3 mg. per 100 c.c. A high concentration does not insure recovery as demonstrated by the fact that in our fatal cases the maximum concentrations were respectively 18 mg., 14 mg., and 11 mg. per 100 c.c.

Deaths

Death occurred in two patients with Type XIV infection. One of these, Case 45 (figure 7), was admitted on the fifth day of the disease with three lobes of the lung involved. Pulse and respiratory rate were disproportionately rapid. Repeated blood cultures showed no bacteremia. Forty-four grams of sulfapyridine were given within four days without effect on temperature or leukocytes. The concentration of sulfapyridine in the blood reached a maximum of 18 mg. per 100 c.c., yet no evidence of toxicity was observed. Although there was an abundance of free sulfapyridine in the blood, it proved ineffective. Type specific anti-pneumococcus serum might well have been given.

The second patient who died, Case 50 (figure 8) with a Type XIV infection was admitted on the fourth day of the disease with consolidation of the lower lobe of the right lung. Bacteremia was demonstrated by two blood cultures. Sulfapyridine produced a fall in temperature and disappearance of the bacteremia in 36 hours. It was given for four days and then discontinued because vomiting was severe. Twenty-four hours later the pneumonic process extended into the upper lobe of the right lung and bacteremia recurred. Simultaneous sulfapyridine and specific anti-pneumococcus serum therapy (100,000 units) was instituted with resulting disappearance of fever. A four day period of clinical improvement was followed by another recurrence of chills and fever. Since pyuria and bacteriuria were found, it suggested that the cause of this relapse was pyelitis. Sulfanilamide was employed instead of sulfapyridine but the temperature continued to be elevated. Cardiac murmurs indicative of aortic insufficiency along with the peripheral vascular signs which accompany such defects, were observed on the fifth day of the recurrence. Type XIV pneumococcic bacteremia was again observed. The patient died eight days after the onset of this relapse and 26 days after admission to the hospital. Postmortem examination revealed acute bacterial endocarditis with extensive

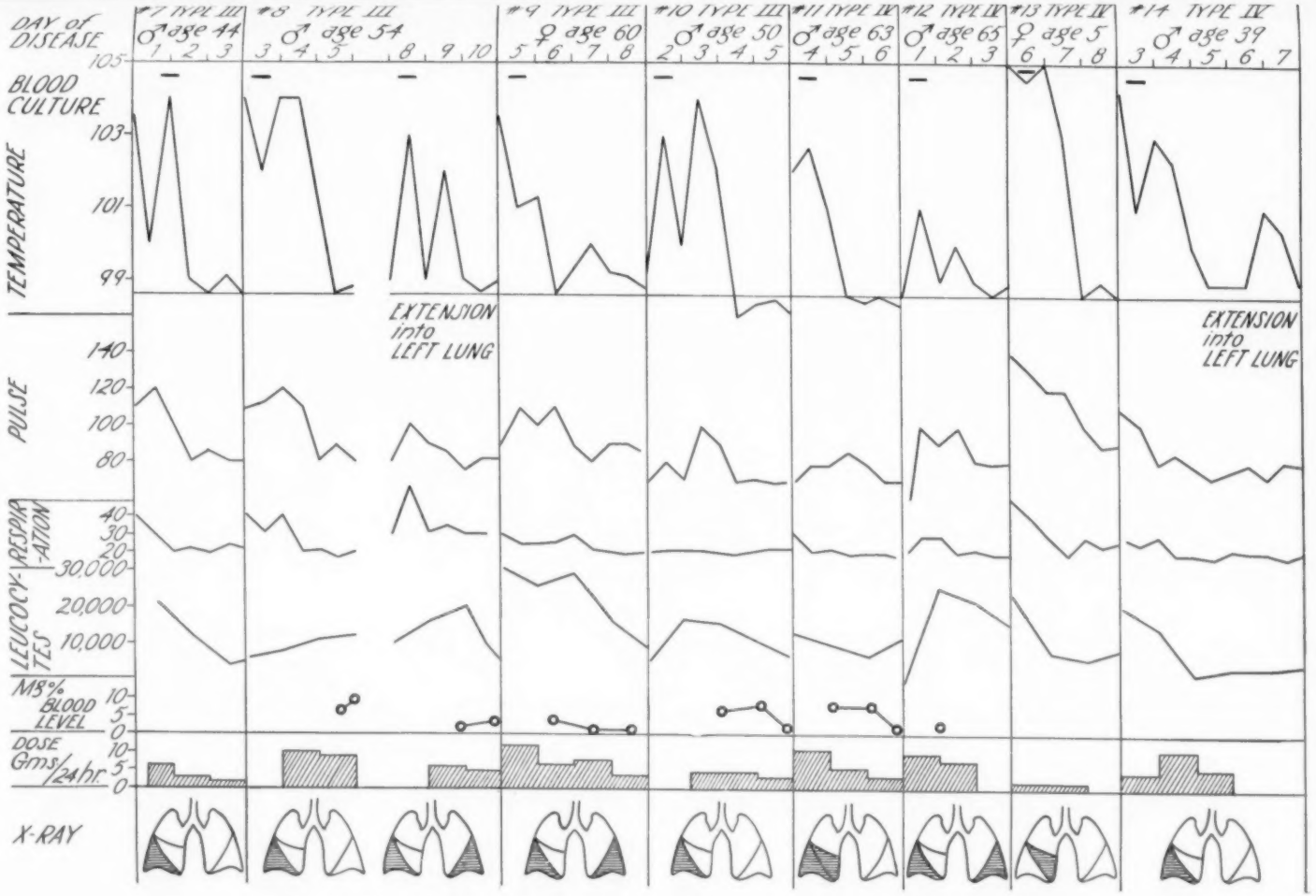

FIG. 2. Clinical summary of four patients with Type III infection and four with Type IV infection.

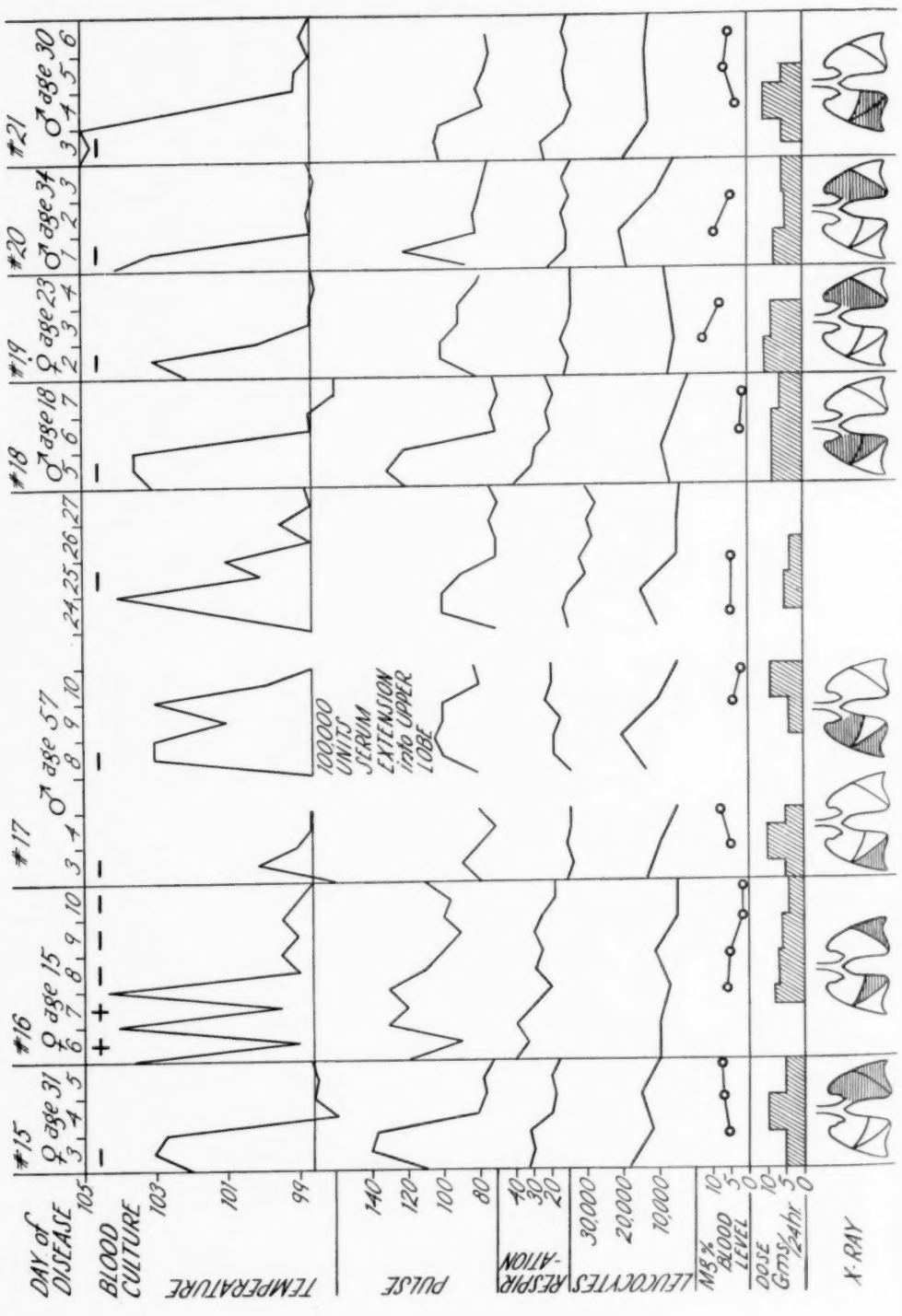

FIG. 3. Clinical summary of seven patients with Type V infection.

necrosis of the cusps of the aortic valve and underlying myocardium. The renal parenchyma was studded with minute abscesses from which Type XIV pneumococci were cultured.

The infection in the third fatal case, Case 46 (figure 7), was caused by a Type V pneumococcus. She had vomited repeatedly since the onset of the disease seven days before admission. Blood cultures were negative. Twenty-three grams of the drug were given in the course of three days, which elevated its concentration in the blood to 14 mg. per 100 c.c. Vomiting continued; the abdomen was rigid and the patient appeared desperately ill. On the fourth day shock occurred suddenly and did not respond to treatment with intravenous sodium chloride, acacia and blood transfusion. Death occurred 24 hours after the onset of shock. Postmortem examination revealed consolidation of the upper lobe of the right lung and a resolving pneumonic process in the lower lobe. An acute ulcer whose histological characters suggested its recent formation was found in the cardiac portion of the stomach. A local fibrinous peritoneal exudate overlay the ulcer which, however, had not perforated into the peritoneal cavity.

FIG. 3. Clinical summary of seven patients with Type V infection.

BACTEREMIA

Seven of eight patients with bacteremia recovered. One patient died as a result of acute pneumococcic endocarditis involving the aortic valve. The bacteremia in four was due to a Type V organism, in three to a Type I, and in one to a Type XIV.

In two of the patients with Type I infections, specific anti-pneumococcus rabbit serum was given prior to sulfapyridine because the supply of the drug was temporarily exhausted. In a patient, Case 50 (figure 8), with Type XIV pneumonia, the initial bacteremia was treated with sulfapyridine and its recurrence with simultaneous sulfapyridine and serum. This combined treatment was used because the patient had not tolerated the sulfapyridine during the 24 hours preceding the onset of the recurrence and because extension of the pneumonia with recurrence of bacteremia had taken place when sulfapyridine alone had been used.

The remaining five patients received only sulfapyridine and in larger amounts (50 to 98 gm. total dose) than patients without bacteremia. This may account for the fact that leukopenia and anemia were observed in two of them.

The recurrence of bacteremia and development of acute bacterial endocarditis in one patient when administration of sulfapyridine was discontinued suggest the desirability of prolonged administration to patients with bacteremia. Within 24 hours after sulfapyridine is begun, the blood stream is often found free of bacteria.

Defervescence was by lysis in six patients in the bacteremic group and in two patients by crisis.

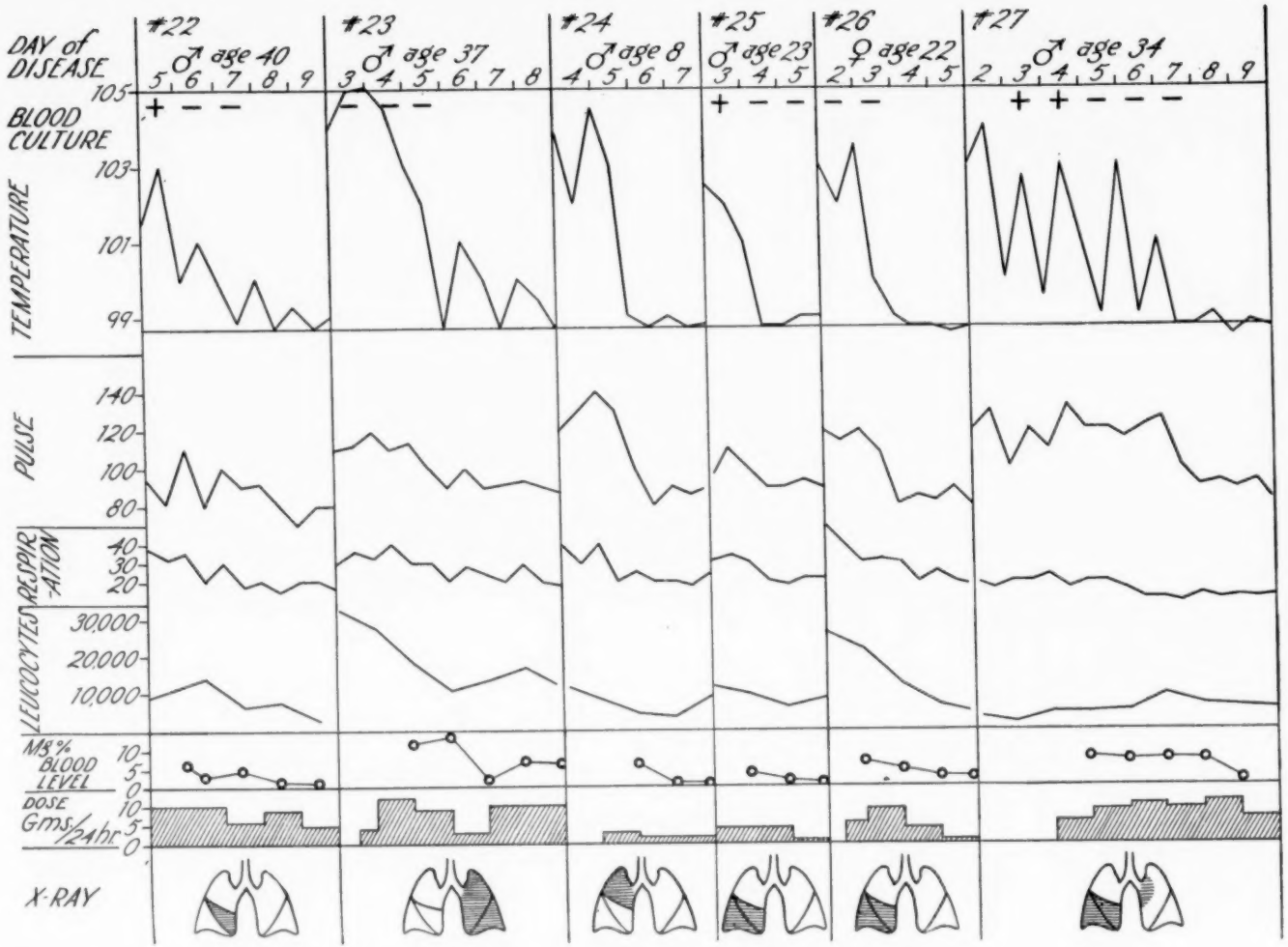

FIG. 4. Clinical summary of six patients with Type V infection.

Empyema

Two patients developed pneumococcic empyema during treatment with sulfapyridine. In both, Cases 48 and 49 (figure 8), the free sulfapyridine was repeatedly observed to be 6 mg. per 100 c.c. in the blood, yet a purulent effusion occurred and organisms which could be typed were cultured from the chest fluid. Surgical intervention ultimately became necessary.

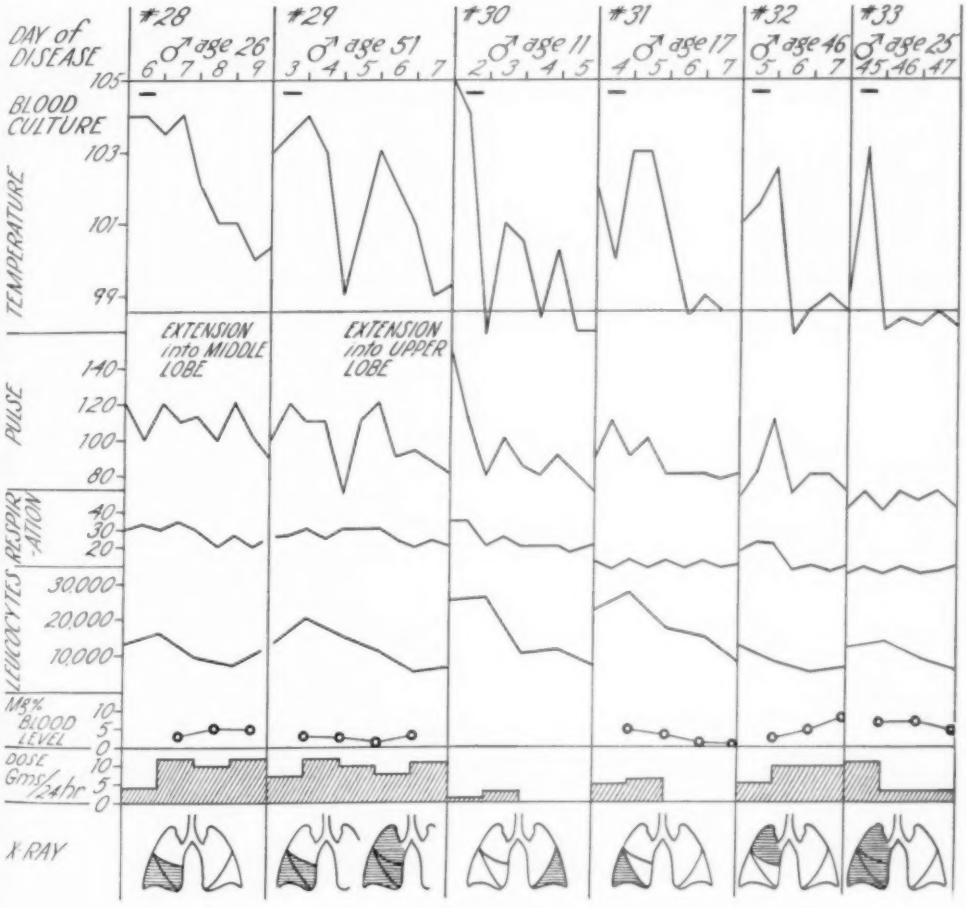

Fig. 5. Clinical summary of six patients with Type V infection.

One patient suffering from an active Type VII infection, Case 33 (figure 5), had had an empyema for 45 days before admission. An immediate response to sulfapyridine occurred (figure 5) before the fluid was aspirated from the pleural cavity. When the blood level of free sulfapyridine was 6 mg. per 100 c.c., its concentration in the fluid aspirated from the chest was 3 mg. per 100 c.c. Repeated aspirations with a large caliber needle were the only method necessary for adequate drainage.

A clear, sterile effusion occurred during the course of pneumonia in three other patients. The fluid did not reappear after a single aspiration.

Extension of Pneumonia

When the fever disappears and the pulse rate returns to normal, the physician tends to feel that the patient is cured. But it is just at this time, in our experience, that he needs sharp observation to detect recrudescence.

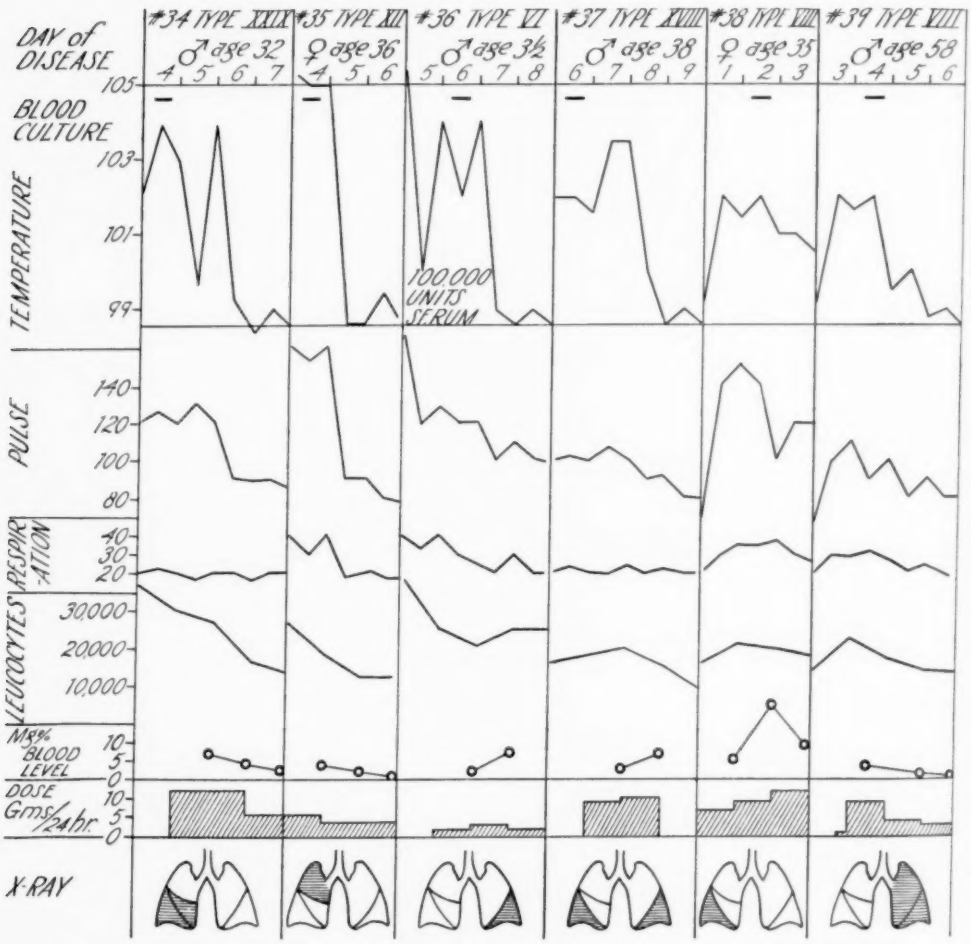

FIG. 6. Clinical summary of six patients with infection of Types XXIX, XII, VI, XVIII, and VIII.

In four patients extension of the pneumonic process occurred after the drug had been discontinued, but in these it had been discontinued not because the patient was considered well, but because of (a) leukopenia (3 patients) and (b) severe vomiting (one patient). Extension occurred in two patients in spite of what appeared to be adequate amounts of sulfapyridine in the blood.

The ability of pneumonia to spread during a period of inadequate treatment with sulfapyridine was illustrated by Case 17 (figure 3). The drug was stopped because of leukopenia. Immune rabbit serum (100,000 units) was given with only transient effect. The leukocytes rose to 21,000 and more sulfapyridine was given following which a prompt fall in temperature was observed. Leukopenia again recurred. A second relapse occurred 13 days later with an increase of leukocytes. Sulfapyridine was again given and although the temperature fell to normal and physical examination indicated subsidence of the pneumonic process, the leukopenia recurred for the third time.

Leukocytes

The effect of sulfapyridine on the leukocyte count was unpredictable. In the majority of patients it paralleled the temperature curve, but there were numerous exceptions to the rule. In eight patients who received comparatively small doses of the drug (less than 30 gm.) the leukocyte count fell to about 3,000, but agranulocytosis did not occur in any of them.

The leukocytes did not decrease rapidly in all patients. In Case 5 the large amount of sulfapyridine given in the first five days produced only a slow decline. In the fatal cases, in spite of high concentrations of sulfapyridine, the leukocyte count continued to increase.

In those patients who had leukopenia on admission, Cases 12, 8 (figure 2), 27 (figure 4), administration of the drug resulted in an increase rather than decrease in the leukocyte count.

It is interesting that all patients with initial leukopenia had a high percentage of polymorphonuclear leukocytes and as the leukocyte count increased the percentage of polymorphonuclear cells decreased. Leukopenia apparently need not necessarily be considered a contraindication for the use of this drug when the etiological agent is the pneumococcus.

Red Blood Cell Count and Hemoglobin

Blood counts and hemoglobin determinations were done on all patients at regular intervals during the period of administration of sulfapyridine, through the courtesy of Dr. Paul J. Fouts of the Lilly Laboratory for Clinical Research. Evidence of anemia which probably was caused by the drug was observed in two patients. In the first one, Case 16 (figure 3), a girl, aged 15, who was desperately ill with Type V pneumonia with bacteremia, 54 grams of sulfapyridine were given in a period of 13 days. The red blood cell count decreased from 4,000,000 with 84 per cent hemoglobin to 2,600,000 with 64 per cent hemoglobin and 8.6 per cent reticulocytes. The leukocytes declined from 10,000 to 4,500. After discontinuing the drug the red blood cell count returned to normal within two weeks without treatment.

The second example of anemia occurred in a patient, Case 49, with a Type III infection complicated by empyema. She received 84 grams of

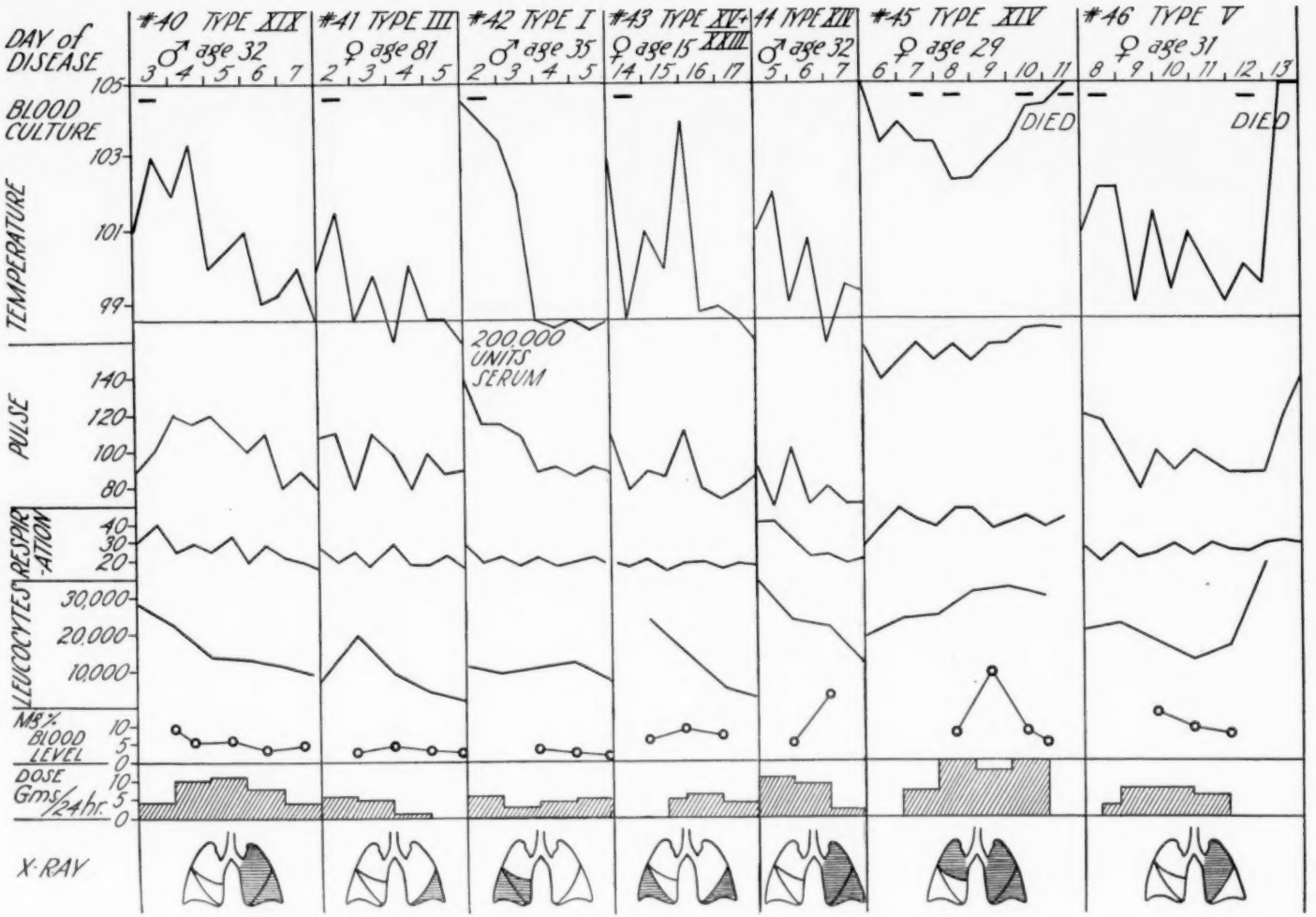

FIG. 7. Clinical summary of seven patients with infection Types XIX, III, I, XV and XXIII, XIV, and V.

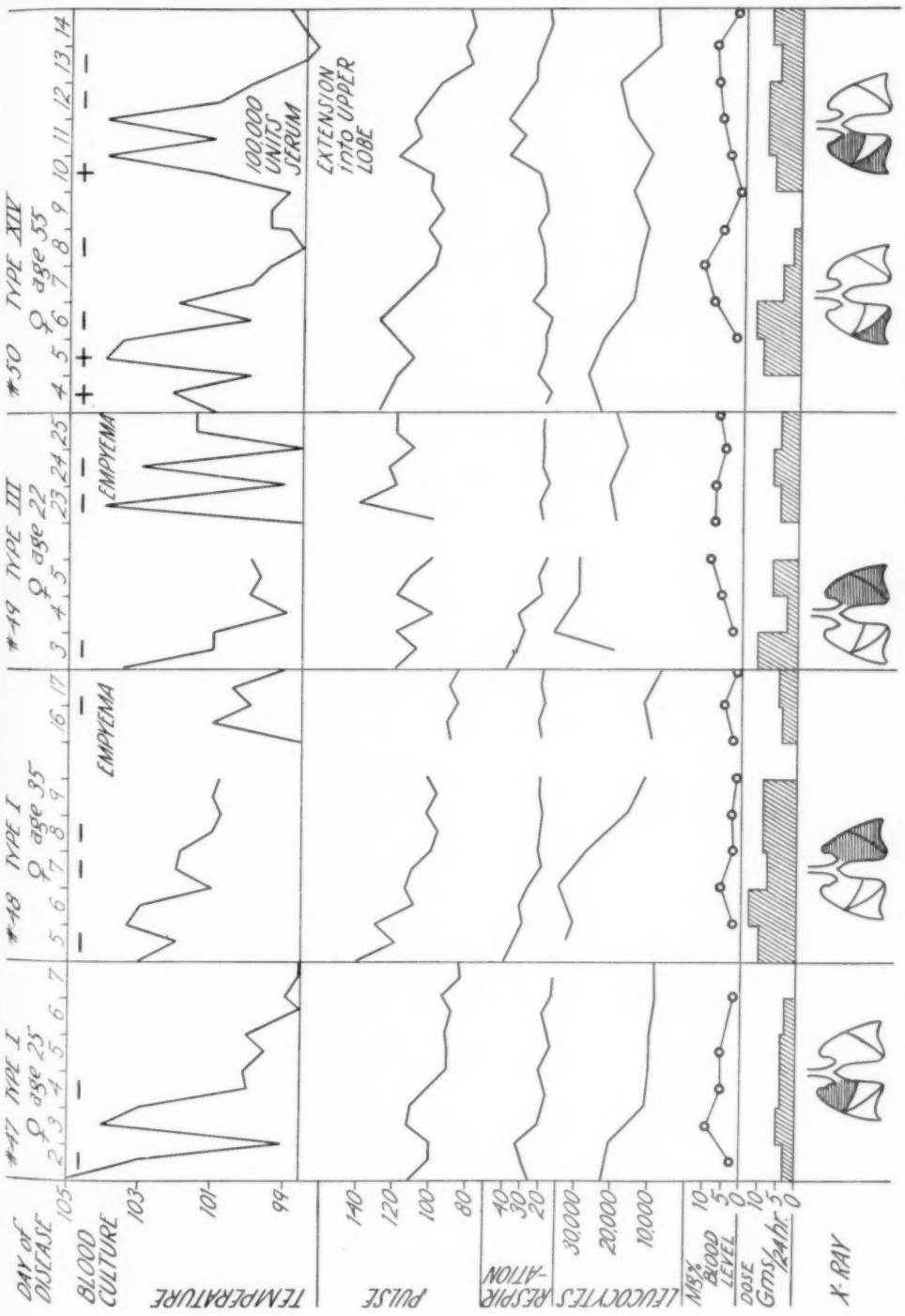

FIG. 8. Clinical summary of two patients with Type I, one patient with Type III and one with Type XIV.

FIG. 7. Clinical summary of seven patients with infection Types XIX, III, I, XV and XIII, XIV, and V.

sulfapyridine in 15 days. The red blood cells decreased from 4,100,000 with 80 per cent hemoglobin to 2,400,000 with 49 per cent hemoglobin. The white blood cell count was 21,000 when treatment was begun and decreased to 16,000.

Effect of Sulfapyridine on the Kidneys

Examination of the urine of patients treated with sulfapyridine suggested that in most patients it had no harmful effects on the kidneys. However, in two patients marked hematuria occurred after large doses. The drug was discontinued and within three days the hematuria abated.

That the drug may be given without necessarily further injuring the kidneys of patients with renal insufficiency is illustrated by Case 47 (figure 8). The infection was caused by Type III pneumococcus, and urea clearance was found to be 10 per cent of normal. After 9 grams of sulfapyridine were given the blood level was 4 mg. per 100 c.c.; the drug was then discontinued because of vomiting. However, the concentration in the blood did not decrease nearly as rapidly as we had learned to expect in patients with normal kidneys. The patient was well on the fifth day after onset of the disease. Urea clearance on the fifteenth day was 14 per cent normal.

Cyanosis

Moderate cyanosis was present in the majority of patients before treatment with sulfapyridine. It could be controlled by oxygen and usually disappeared after crisis occurred. At no time was cyanosis observed comparable to that commonly noted after large doses of sulfanilamide. We found no correlation between cyanosis and the onset of other signs or symptoms associated with the toxic action of the drug.

Discussion

The mortality from pneumococcic * pneumonia in patients receiving no specific treatment in this hospital for the past two years has been 48 per cent (197 patients) and 33 per cent (147 patients) respectively. There is no reason to suppose that it would have been less this year. We have seen few of the so-called "virus" pneumonias which appear to be common in the eastern states. In the 50 patients receiving sulfapyridine the mortality was only 6 per cent, yet 17 of the patients were over 40 years of age. The onset of the pneumonia was three or more days before treatment was begun in 23 patients; six were infected with Type III pneumococci and bacteremia occurred in eight patients. The patients were treated on open wards of a hospital for the indigent without special nursing care. This result, in our opinion, leaves little room to doubt the value of the treatment.

When treatment is begun early, clinical improvement is usually surprisingly rapid and clearing of the morbid changes in the lungs soon follows.

* The bacteria were not typed in all of these patients.

The longer the interval before treatment, the slower this resolution despite the fact that fever may disappear with equal celerity.

The complications attending the use of the drug were few and for the most part not serious except for vomiting and nausea. These occurred in most of the patients, but became important in less than a quarter of them. Anemia and hematuria were unusual.

The response of the leukocytes was unpredictable, although in many patients their number paralleled the temperature curve. The leukocytes continued to increase in our fatal cases in spite of high concentrations of free sulfapyridine in the blood. This may be of some prognostic significance. Our data (figures 2–4) do not indicate, as might have been expected, that leukopenia is a definite contraindication for the use of the drug. Indeed, the leukocytes rose from an initial low level after starting treatment in three patients. It seemed desirable to discontinue treatment because of increasing leukopenia in another three patients. It is interesting that all patients with initial leukopenia showed high percentages of polymorphonuclear leukocytes and that as the leukocytes increased in number their percentage decreased.

Too early withdrawal of the drug may be followed by spread of the pneumonic process. It has been our practice when temperature and pulse return to normal to reduce the dose to 5 grams a day and continue this for three days. Recrudescence is treated by raising the dose to 10 grams a day for 24 to 48 hours. It has been found to be a matter of the greatest importance to examine the patient with care when the fever has disappeared to be sure of resolution.

Bacteremia did not prove to be as serious a handicap in patients treated with sulfapyridine as is usual in patients receiving no specific therapy. One of eight patients died and this one had pneumococcic endocarditis.

We have found it desirable to employ antipneumococcus serum in a few patients in conjunction with the drug chiefly for two reasons, namely, nausea and vomiting and leukopenia. It appeared that we would have been seriously handicapped in our management of these cases had not serum been available.

Empyema developed under treatment in two patients, who later required surgical drainage. Of interest is the fact that fluid aspirated from the chest of a patient with a blood level of 6 mg. per 100 c.c. of free sulfapyridine, contained 3 mg. per 100 c.c. of the drug. It is possible that the relatively free diffusibility of sulfapyridine aids in bacteriostasis in exudates.

We are aware that excessively large doses of sulfapyridine in animals may lead to formation of concretions in the urinary tract. Further, renal damage might result from the clearance of such large amounts of a pyridine-containing drug. Actually no serious damage to the kidneys has been observed in our patients as measured by urea clearance and routine examination of urine specimens. Whether nuclei for future stones have been left in the urinary tract cannot be foretold.

Summary

(1) Fifty patients suffering from pneumococcic pneumonia have been treated with sulfapyridine, of whom three died. The mortality in patients receiving no specific therapy in the previous two years was 48 and 33 per cent. Seventeen of the patients were over 40 years of age; three or more days had elapsed since the onset of the disease in 23 patients; bacteremia occurred in eight patients; one lobe was consolidated in 16 patients, two lobes in 29 patients and three lobes in five patients. Empyema was observed in three patients and sterile effusion in three.

(2) No strict relationship was observed between the level of sulfapyridine in the blood, the amount administered, and the occurrence of toxic manifestations. The manifestations of toxicity were: (a) moderate to severe nausea and vomiting in about 80 per cent of the patients; (b) occasional leukopenia; (c) rare anemia; (d) hematuria.

(3) The response of the leukocytes was unpredictable, but in most cases paralleled the temperature curve. In fatal cases they may continue to rise in spite of high concentrations of the drug in the blood. Initial leukopenia does not necessarily contraindicate the use of sulfapyridine since the leukocytes may rise after its administration. It seemed wise to discontinue treatment in three patients because of increasing leukopenia.

(4) Specific antipneumococcus serum was employed in conjunction with drug therapy chiefly because of the occurrence of (a) leukopenia; (b) nausea and vomiting; (c) hematuria.

(5) One of eight patients with bacteremia died of pneumococcus endocarditis (Type XIV). Larger than usual doses of sulfapyridine were given these patients and the drug was continued longer because bacteremia recurred in one patient after early discontinuance.

(6) Empyema requiring surgical drainage occurred in two patients after sulfapyridine treatment. The concentration of free sulfapyridine in the pleural fluid was about half that in the blood. Sulfapyridine in the exudate may aid in preventing the growth of bacteria in it.

(7) Three patients died and in two of these the infecting organism was Type XIV. The concentration of free sulfapyridine in the blood was kept at high levels, but appeared powerless to arrest the infection. The third patient suffered from a Type V infection, which was controlled by the drug in spite of the fact that treatment was not begun until seven days after onset. Shock occurred on the eleventh day and the patient died a day later. An acute ulcer was found in the cardiac portion of the stomach.

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THE AMERICAN BOARD OF INTERNAL MEDICINE AFTER FOUR YEARS; ORGANIZATION, PURPOSES, AND THE EFFECTS OF SPECIAL BOARDS ON MEDICAL EDUCATION AND PRACTICE *

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When the American Board of Internal Medicine was organized, many of us thought that if what we had in mind could influence favorably the quality of medical preparation and practice in perhaps ten or fifteen years, the effort would be well worth while. However, the effects on younger men entering medicine have been immediate and startling in scope.

In almost every large hospital many interns are now talking not about how soon they can get into practice, but about what more they can do, either by residencies, further basic science training or in positions of part time practice to qualify themselves to be better doctors. Many influences in medical education have been at work, but the operation of special boards has contributed much of the impetus to the advance in graduate medical education. You may be interested in hearing of the work of the American Board of Internal Medicine, whose organization was initiated and underwritten by the College, and of its present and future relation to graduate medical education as the Board and College conceive it.

Organization

The American College of Physicians through its Board of Regents on April 30, 1935, adopted a resolution for the establishment with the Section on the Practice of Medicine of the American Medical Association of an "American Board for the Certification of Internists." The Section on the Practice of Medicine adopted a similar resolution in June 1935, and a joint committee of nine members appointed by these two bodies met for preliminary organization in Philadelphia December 14, 1935. After approval by the Advisory Board the final organization was effected and articles of incorporation filed on February 28, 1936. Final approval of organization was given by the College, by the Council on Medical Education, and by the Section on Practice of Medicine at the annual meetings following. The first meeting of the Board was held on June 14, 1936, under the chairmanship of Dr. Walter L. Bierring. Membership on the Board as finally determined consists of five members from the College, and four from the Section on the Practice of Medicine.

Among the major problems of the Board were the establishment of a list of internists entitled to certification without examination, upon application

* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

prior to July 1, 1937; the formulation of an advisory memorandum of recommended preparation for applicants for examination; plans for written and oral examinations. The preparation of the list of those certified without examination entailed an enormous amount of work, in which the Board availed itself of the invaluable advisory assistance of members of the Association of American Physicians. No doubt the Board has committed some errors of omission, but these have been unintentional, and in the main have occurred by reason of the inaccessibility of evidence. They have been in large part corrected.

Thus far 1800 have been certified without examination and 358 certified by examination.

Graduate Medical Education

Before passing to a more detailed consideration of the work of the Board, we may digress a moment to comment on the general problem of Graduate Medical Education as it affects the work of the Board. When the prospective doctor decides to enter the profession of medicine as a life work, he directs his premedical studies to comply with the entrance requirements of the medical school and then follows the prescribed medical curriculum and serves an internship, all in compliance with curricular and legal provisions. He then passes the examinations of a State Board or their equivalent and is admitted to practice. While he may do additional voluntary work in preparation, the larger part of his study has been necessary to comply with the demands of the police power of the State. In contrast to the undergraduate period, any further graduate study including preparation for board examinations is entirely voluntary. The content also of these graduate studies is optional, although experience shows that certain types of study are likely to fit the needs of most candidates and are therefore recommended. As in any other field of education, there will be dissimilar views, diverse types of intellectual fitness, and varying degrees of the will toward scholarship. All that graduate medical education can or should attempt to do is to furnish guidance and opportunity. Compulsion and regimentation have no place here. Democracy in medicine like democracy in political fields depends on the acceptance of personal responsibility by the individual. Initiative and sense of responsibility must be stimulated in the individual if we are to avoid the dangers and stunting effects of paternalism.

With the rapid expansion of the field of medicine it has become no longer possible for one man to acquire even a moderate knowledge of the entire field, and the necessary division into special fields has resulted in an ever increasing number of legitimate subdivisions, expertness in each of which requires a life time of experience.

The medical work of the world must be done by many hands and at many levels. Work at each level is well worth while, and offers abundant satisfactions to him who does his job well. Nor should there be any attempt to dictate how many men should be allotted to one or another group or level.

Though often forgotten in these days, the economic laws of supply and demand are inexorable in medicine as in the production and marketing of corn. And in medicine, as they have proved in agriculture, attempts artificially to modify the operation of these laws can have only a temporary and often ultimately a deleterious effect.

The educational needs of these several levels differ just as the economic needs of communities differ. Neither can be supplied by general legislation. There is required individual level planning just as there is necessary economic regional planning.

At the moment, we are concerned with those who desire to qualify themselves especially in internal medicine. This group is comparatively small at present, when we consider the great body of physicians who prefer to engage in general practice, a field of action of much larger importance to medicine as a whole. It is perhaps not an idle hope that as the years go on, many of those who have elected first to acquire an understanding of medical problems in the school of practice may wish later to add to their store of knowledge from other sources. Medical experience in practice is essential to the attainment of full medical stature, but the rapid expansion of medicine whereby its borders touch on a multitude of ancillary subjects not recognized as important a few years ago, has complicated the problem of the young physician. He must exercise special care not to be drawn so far into the responsibilities of practice in his early years that he loses his facility in other technics just as necessary for his continued growth.

Requirements of the Board

The requirements of the Board for admission to examination as outlined in the published brochure are designed as a guide to the type of preparation which the board believes will best fit the candidate for the examination, and much more important, will enable him to progress far, and to take a worthy part in the advances in medicine of the future.

A few quotations will illustrate the spirit and intent of these recommendations: "The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad general principles for training, however, may be outlined although such suggestions as are made must of necessity be subject to constant changes reflecting the dynamic nature of the specialty."

"A sound knowledge of physiology, biochemistry, pharmacology, anatomy, bacteriology and pathology as they apply to disease is essential for continued professional growth of the individual who practices internal medicine. Such knowledge may be acquired in a number of ways." These include residencies with adequate educational opportunities, graduate work in basic sciences closely integrated with clinical facilities, and service in well organized clinics or in preceptorships.

Residencies in well ordered hospitals afford continued clinical contacts and at the same time opportunity for the further acquirement of funda-

mental basic technics under the guidance and inspiration of older men. Such residencies while perhaps safer for the average younger man who is entering the critical first five years of his medical career, are by no means the only avenues by which he may travel toward the medical scholastic goal. He may already have a definite prospective goal of accomplishment in mind, and to this end may require one or more years of special basic preparation, or, as is perhaps more likely, he may still be searching for the precise line along which he shall go. Medicine is expanding rapidly and his final decision may have to wait. In the meantime, a careful choice of his medical associations, perhaps in the nature of a preceptorship or in a clinic with a practical but scholarly atmosphere will fit his needs. There is no one road, and if there were such, to require all men to travel it would dwarf the growth of many a choice spirit destined in freer surroundings to a high place in medicine.

"The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have training in their use." This implies practical experience, with emphasis on the concepts of the experimental method, under the guidance of older men who bring to their clinical problems ripe knowledge and clinical judgment.

"Although it is required that at least five years must elapse between the termination of the first intern year and the date when the candidate is eligible to take the examination, a longer period is advisable."

For many candidates an examination which, taken after the minimal five years training would be an anxious period, would, taken after seven or eight years, be an interesting and perhaps even an enjoyable experience.

"Time and training are but a means to the end of acquiring a broadness and depth of knowledge of internal medicine." "The responsibility of acquiring the knowledge as best he may rests with the candidate; while the responsibility of maintaining the standard of knowledge required for certification devolves upon the Board."

It may again be noted that these suggestions are advisory only. No doubt some candidates will appear with quite different but nevertheless adequate preparation. We are reminded that Robert Koch might have had difficulty in qualifying before a board in his time. Emphasis should be on standards rather than on standardization. A reasonable amount of organization and definition is required, however, to make realization of standards possible.

The Examination

The examination consists of a written Part I which is held simultaneously in different regions of the United States and Canada on the third Monday of February and October of each year.

Section A includes questions in the basic sciences as related to internal medicine; Section B consists of questions in general internal medicine. Candidates successful in Part I are eligible for the practical or clinical examination (Part II) which is conducted by members of the board assisted by addi-

tional examiners, near the time and place of the annual meetings of the College of Physicians and of the American Medical Association.

Papers are known by number only. The papers are read by members of the Board and failing or doubtful papers are read by two and if necessary by a third member. This has entailed the expenditure of much time and effort. The thought uppermost with the Board has been that of maintaining fairness, of a realization of what the result means to the candidate, and of maintaining a high standard of performance.

Certain clinical questions involving for example the interpretation of physical signs and symptoms in a case history have elicited answers, some right, some wrong. In giving a wrong answer the candidate may have taken the wrong turn at a critical point or misinterpreted the relative importance of facts as related in the question, and yet at the same time may have shown excellent ability in reasoning and in correlating his data as he understood them. On the other hand, a candidate may stumble on the right answer and yet show himself woefully weak in ability to correlate and interpret facts. The wrong answer may call for a better grade than the correct answer. I hasten to note, however, that the Board would not wish to put a premium on wrong answers.

Failures in examinations are directly attributable to inadequate preliminary training and insufficient experience. Some candidates who were refused admission to examination on these grounds were later admitted after two years further preparation and were successful in the examinations; other candidates whose records indicated what might be expected to be adequate training, were deficient both in factual information and in the ability to reason out clinical problems. In general the well trained candidate experienced but little difficulty.

Those who are inclined to regard some questions asked by the Board as too technical, and in the nature of catch questions, may forget that this is not an examination to test minimal standards for licensure but rather to ascertain the acquirement of the broad knowledge which may reasonably be expected of him who assumes to have a superior knowledge of the practice of medicine.

Special Groups in Internal Medicine

Until quite recently the multiple duties of the Board of Internal Medicine prevented its taking up the important matter of representation in the work of the Board of certain of the sub-specialties in internal medicine, such as cardiology, gastroenterology, tuberculosis, allergy, etc. Many of the leaders in these fields are already certificants of the Board, but they feel, and the Board agrees, that recognition should be given to these special sub-groups. The Board believes that all candidates in sub-specialties should have a broad foundation in internal medicine, and that therefore they should be prepared to pass the examination outlined in Parts I and II. In the practical examination the Board will invite representatives from lists nominated by the cor-

responding sub-specialty to sit with the Board, and examine candidates in subjects of the special field. The certificate will bear an appropriate notation of proficiency in the sub-specialty.

The Relation of Special Boards to the General Problem of Medical Education

The immediate field of the Board of Internal Medicine is a relatively limited one, but its problems are similar to those of other boards, and its influence in raising standards is naturally correlated with that of other agencies in graduate medical education. In time it will assist in raising the level of under-graduate medical education by setting standards of scholarship toward which the young student may strive.

Special boards may at times take too narrow a view of their own specialties. Their function is not to tell a man what he should do, but rather to suggest how he may do it better. Special fields of medicine are not closed boxes. Their borders are better defined only in general terms, and attainment in each field stems from a necessary broad knowledge of the fundamentals of medicine. An internist should not hesitate to look at a retina, and an expert gynecologist should be qualified to deal with whatever he finds on opening the abdomen. Those directing the activities of special boards would do well to avoid jurisdictional quibbles and be guided rather by what is best for American Medicine.

Some hospitals have considered making certification by special boards a prerequisite for staff appointments. This is of course a question of hospital policy, with which the boards have no concern. The acquirement of certification is voluntary, and the Boards are interested only in standards. The hospital may wish to avail itself in many instances of the judgment of the Boards, but at the present time there are many men, especially of the older group, who are well prepared, but who have not wished to apply for certification. The conditions and needs peculiar to each community should be considered in the determination of local policy.

Coöperation with Other Agencies

Encouraging progress has been made in establishing active coöperation between the agencies charged with the several phases of medical education. The quality of residencies and similar graduate educational opportunities concerns the American College of Physicians, the Council on Medical Education and the Board of Internal Medicine. The Council on Medical Education and Hospitals has extended its field from that of undergraduate medical schools and internships, in which it has accomplished so much in the past 35 years, to now include hospital activities in the graduate field. During the past year a coöperative committee of two representatives of each group has been established to secure the necessary data for ascertaining the quality of residencies, utilizing the organization already operating under the direction

of the Council on Medical Education. By June 1940 ten of thirteen special boards will have lists of approved residencies identical with those of the Council.

Recently a commission on Graduate Medical Education representing agencies concerned in medical education including Medical Schools, Hospitals and State Boards has completed a report which will be of value in indicating requirements and standards in this increasingly complex field.

The action of the Regents of the College in making certification by the American Board of Internal Medicine a prerequisite for promotion from associate to fellow in the College is a further evidence of the interest of the College in promoting medical scholarship and is a gracious recognition of the work of the Board.

In its arduous work the Board has been ably supported by the College, the Council on Medical Education and Hospitals, and by the American Medical Association. There are many fields of service in American medical life, of which we occupy only a small part. We wish to be of service to all, especially to that great body of general practitioners who carry the real load. Although we might sometimes like to think otherwise, men differ in tastes and ideas, in the type of their original mental equipment, and in their ability and willingness to work, sometimes for long periods without reward. Judgment as to his own special aptitudes for one or another kind of specialized work also plays a part in determining the ultimate field of activity and the attainments of the physician. The Board conceives its functions to include the encouragement of men to acquire a broad educational foundation both cultural and scientific, to reason carefully, to engage in long term planning, to work diligently, to the end that they may improve the quality of medical care of patients and contribute to a superior standard of American medical scholarship.

CASE REPORTS

THE COEXISTENCE OF TOXIC HEPATITIS, ACUTE HEMOLYTIC ANEMIA AND RENAL DAMAGE FOLLOWING SULFANILAMIDE THERAPY; REPORT OF TWO CASES *

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IN 1937 Harvey and Janeway [1] first described acute hemolytic anemia as a toxic manifestation of sulfanilamide therapy. They presented three cases in adults. Shortly thereafter Kohn [2] and Willis [3] each presented a case in an infant. Wood [4] studied 522 patients, 144 children and 378 adults, receiving sulfanilamide and found that 21 developed acute anemia. Of these, 12 or 8.3 per cent were children, and nine or 2.4 per cent were adults. Long, Bliss and Feinstone [5] in their study of 307 adults and 101 children found the incidence 2.9 per cent and 8.9 per cent respectively. In 1938 Bannick, Brown and Foster [6] first mentioned hepatitis as another evidence of sulfanilamide toxicity. That same year Garvin [7] presented five cases as examples of this manifestation. However, in 1937 Hageman and Blake,[8] in describing a febrile reaction to sulfanilamide, had presented one case which showed a toxic hepatitis, but had not pointed this out as a reaction to sulfanilamide. The combination of toxic hepatitis and acute hemolytic anemia has not hitherto been described as a complication of sulfanilamide administration, with the possible exception of an unproved case by Garvin.[7] Furthermore, Ottenberg [9] noted that kidney damage is not mentioned in the literature as one of the toxic manifestations of sulfanilamide and records one case of marked albuminuria; the urine in his case also showed a few red blood cells on two occasions. He also described two cases of marked renal insufficiency in association with marked hemolytic anemia, hemoglobinuria and jaundice. The following two cases are examples of the coexistence of these toxic effects.

CASE REPORTS

Case 1. A 55-year-old dress operator was first seen by his physician at noon on December 15, 1939, because of fever, chills and redness and swelling of his face. His temperature was 105.2° F. and he was found to have a facial erysipelas for which he was given sulfanilamide 15 grains, with sodium bicarbonate, every three hours. During the night he vomited and had diarrhea. He was seen at noon the following day, December 16, at which time the temperature had fallen to 99.6° F., the face lesion was the same, and the sclerae were faintly yellow. The sulfanilamide was immediately discontinued, the patient having had a total of 70 grains (60 grains on December 15 and 10 grains on December 16). At this time the hemoglobin was 70 per cent Sahli (10.1 gm.), the red blood cells were 4,400,000 and the white blood cells

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From the Medical Services of Dr. Henry Schumer and Dr. Emil Koffler, The Bronx Hospital, Bronx, New York.

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19,950 per cubic millimeter. The urine had a faint trace of bile, and urobilinogen was present in a dilution of 1 to 20 but absent in a dilution of 1 to 40. On December 17 he complained of pain in the right upper quadrant of the abdomen. His physician found that the temperature had remained under 100° F., and that the face lesion was definitely improved, but that the icterus of the sclerae was deeper and seemed to be present also in the skin, and that there was mild percussion and palpation tenderness in the right upper quadrant of the abdomen. Hospitalization was advised and the patient was admitted to the medical service of Dr. Henry Schumer on December 17 at 4 p.m.

At this time he appeared subacutely ill, with a rectal temperature of 99.2° F. There was erythema and moderate desquamation of the skin of the forehead and cheeks, with slight swelling. The sclerae were icteric and there was mild icterus of the remainder of the body. The mucous membranes of the hard palate and posterior pharynx exhibited a yellowish tinge. The liver was not palpable. The remainder of the physical examination was normal.

Course: The patient was started on a continuous infusion of 5 per cent glucose in physiologically normal saline containing 50 mg. of vitamin B_1 per 1000 c.c. of fluid, and had received 1300 c.c. when this therapy was discontinued the following day. It was replaced by a high-carbohydrate, low-fat diet. The blood chemistry on December 18 revealed glucose of 134 mg. per cent, urea nitrogen 23.1 mg. per cent, uric acid 4 mg. per cent, cholesterol 217.4 mg. per cent of which 114.4 mg. per cent or 53 per cent of the total were esters; the total protein was 5.62 grams per cent. The stool was faintly positive for bile but was negative for blood. The hippuric acid test showed 2.4 grams of benzoic acid recovered as hippuric acid in five hours (normal is 3 grams or more). The urine was amber, acid with a specific gravity of 1.018; sugar, albumin and acetone were absent, and the microscopic examination was negative. The admission icteric index was not determined due to the loss of the blood sample.

The jaundice was clinically absent by December 20, at which time the icteric index was 7.0 and the Van den Bergh reaction was direct delayed with a serum bilirubin of 0.5 mg. per 100 cubic centimeters. Urobilinogen was present in the urine in a 1 to 80 dilution and there was a faint trace of bile in the urine. A blood study on December 19 showed a hemoglobin of 50 per cent Sahli (7.3 gm.) with 2,820,000 red cells, total leukocytes 11,300, with a differential of 66 neutrophiles, 1 basophile, 10 band forms, 20 lymphocytes and 3 monocytes. The morphology of the red blood cells was normal. The blood sulfanilamide concentration on December 18 was less than 0.5 mg. per cent. The urine on December 19 was rec and contained numerous red cells; urines repeated on six occasions showed red cells present five times, ranging from 2 to 3 per high power field up to "numerous." On December 21 the blood hemoglobin was 48 per cent Sahli (7 gm.) with 2,420,000 red cells per cubic millimeter. On December 22 the urobilinogen in the urine decreased to positive in a 1 to 30 dilution with a very faint trace of bile remaining. On December 23 the prothrombin time (Smith's method) was 100 per cent of normal. The fragility of the red cells was determined December 23 and revealed hemolysis to begin at 0.42 per cent and to be complete at 0.30 per cent. On December 24 the hemoglobin was again 48 per cent Sahli (7 gm.) and the red cells were 2,770,000 per cubic millimeter.

The patient was given a transfusion of 500 c.c. of citrated blood on December 25. Following this the hemoglobin and red cells increased; on December 26 the hemoglobin was 66 per cent Sahli (9.6 gm.) with 3,820,000 red cells and leukocytes 7,900 per cubic millimeter. The differential count showed 73 neutrophiles, 7 band forms, 12 lymphocytes, 6 monocytes, 1 eosinophile and 1 Turck cell per hundred cells.

The icteric index on December 28, the day before discharge, was 10.3, the Van den Bergh reaction was direct delayed and there was 1.0 mg. per cent of serum bilirubin. The hippuric acid test on this day showed 3.4 grams of benzoic acid excreted

as hippuric acid in five hours. Urobilinogen was present in a dilution of 1 to 30 and bile was absent from the urine.

The morning of the day of discharge the urea nitrogen was found to have decreased to 16.3 mg. per cent, the uric acid to 3.1 mg. per cent, and the total protein to have risen to 6.9 grams per cent.

The temperature remained normal throughout the duration of hospitalization. The facial lesion disappeared by December 22. On December 29 the patient was discharged, much improved.

The patient returned January 8, 1940, ten days after discharge, for a blood study. At this time his hemoglobin was 76 per cent Sahli (10.9 gm.), the red cells were 3,900,000 and the total leukocytes 6,700 per cubic millimeter. The differential count showed 60 neutrophiles, 2 band forms, 5 eosinophiles, 1 basophile, 31 lymphocytes and 1 monocyte per hundred cells. The reticulated erythrocyte count was 0.9 per cent.

He returned again on January 22, 1940, at which time his hemoglobin was 90 per cent Sahli (13 gm.), the red cells were 4,710,000 and the white cells 9,500 per cubic millimeter, with normal differential count and reticulocytes of 1.4 per cent. The urine was entirely normal and urobilinogen present in a 1 to 20 dilution.

The laboratory findings are summarized in the accompanying chart.

Comment

The case presented has several features of interest. About 12 hours after therapy was started early toxic symptoms in the form of vomiting and diarrhea were noted. Within 24 hours, after 4.6 grams of the drug had been taken, jaundice was noted, and this progressed. At this time a blood count revealed a mild anemia and a faint trace of bile with normal urobilinogen in the urine. In view of the urinary findings, the jaundice, and the absence of hemolysis of red cells a toxic hepatitis must have been present at this stage. This was borne out by the pain and tenderness in the right upper quadrant, the diminished hippuric acid excretion and the low serum protein concentration; it was further confirmed by the return to normal of these findings by the time of discharge. The hepatitis was of mild degree since the jaundice cleared in five days, though the urine contained bile for some days later. The hepatitis was probably prolonged by the anoxia consequent upon the subsequently developed hemolytic anemia which reached its maximum five days after sulfanilamide was discontinued. In spite of the marked and rapid hemolysis there was no rise in temperature, only a slight leukocytosis and polynucleosis, and no change in the morphology of the red cells, features which have been considered as pathognomonic of acute anemia due to sulfanilamide (*vide infra*). The anemia responded dramatically to transfusion and one month later the blood count was normal.

The elevated urea nitrogen, which returned to normal by the time the patient was discharged, and the repeated presence of red cells in the urine noted on microscopic examination may have been due to some renal irritation or damage. The grossly red urine which was found at the height of the hemolytic process may have been due to hemoglobinuria, though no spectroscopic examination was done. Whether the kidney injury in the present case was due to sulfanilamide per se or to the presence of bile in the blood cannot be decided.

Case 2. A 30 year old white male was admitted to the medical service of Dr. Emil Koffler on April 2, 1940, because of marked painless jaundice which had begun the day before admission. The patient became ill on March 30, 1940, with a sore throat, generalized aches and pains and temperature of 105.5° F. His physician

CHART I

Case 1

	12-16-39	12-18-39	12-19-39	12-20-39	12-21-39	12-22-39	12-23-39	12-24-39	12-25-39	12-26-39	12-28-39	12-29-39	1-8-40	1-22-40
BLOOD														
Hemoglobin (Sahli)	70%		50%		48%			48%		66%	75%		76%	90%
Hemoglobin grams	10.1		7.3		7.0			7.0		9.6	10.8		10.9	13.1
RBC (millions per cu.mm.)	4.4		2.82		2.42			2.77		3.48	3.82		3.9	4.71
WBC per cu.mm.	19,950		11,300								7,900		6,700	9,500
Polys per 100 cells			66								73		60	51
Bands per 100 cells			10								7		2	0
Lymphs per 100 cells			20								12		31	40
Reticulocytes										5.2%			0.9%	1.4%
Fragility							0.42% to 0.30%							
Icteric index				7.0							10.3			
Serum bilirubin mg. %				0.5							1.0			
Van den Bergh				Direct Delayed							Direct Delayed			
Prothrombin time (Smith's method)							100%		Transfusion—500 c.c.					
Chemistry														
Urea nitrogen (mg. %)		23.1										16.3		
Uric acid (mg. %)		4.0										3.1		
Cholesterol (mg. %)		217.4												
Cholesterol esters (mg. %)		114.4												
Total protein gm. %		5.62										6.9		
Sulfanilamide conc. (mg. %)		<0.5												
URINE														
Appearance		Amber	Red	Yellow	Cloudy Amber	Amber				Straw		Amber		Yellow
Urobilinogen (highest positive dilution)	1:20			1:80		1:30				1:30				1:20
Bile				Faint trace		Very faint trace				Absent				
Microscopic		Neg.	Numerous red cells	2-3 red cells	Numerous red cells	Occ. RBC				8-9 red cells		2-3 red cells		Neg.
HIPPURIC ACID SYNTHESIS														
Total amount excreted in 5 hours calculated as benzoic acid gm.		2.4								3.4				

found an acute pharyngitis for which he prescribed sulfanilamide. The drug was administered for the first time at 10 p.m. of that evening (March 30), a total of 90 grains being given between March 30 and March 31. The temperature the evening of March 31 was 100.5° F., and the patient felt much improved. A blood count on March 31 showed 4,500,000 red blood cells, with a hemoglobin of 85 per cent Sahli (12.3 gm.) and 28,000 white blood cells, with a differential of 90 neutrophiles, 4 band forms and 6 lymphocytes. Twenty grains more of sulfanilamide were administered, the last dose being given at noon of April 1, bringing the total amount to 110 grains. He continued to feel improved except for slight nausea, occasional abdominal cramps and five loose bowel movements on April 1. The stools were black (the patient had been receiving oral iron medication since April 1) and his urine was dark brown in color. The patient was seen by his physician on April 1 at 10 p.m., at which time no jaundice was evident. On April 2 the family of the patient noticed that he was jaundiced; the physician confirmed this observation. At noon of April 2 a blood count revealed the hemoglobin to be 55 per cent Sahli (8.0 gm.), red blood cells 3,900,000, leukocytes 20,800; with a differential count of 76 neutrophiles, 2 band forms, 16 lymphocytes, 5 monocytes and 1 eosinophile. Fifty cubic centimeters of a 50 per cent solution of glucose were given intravenously, following which he had a chill and his temperature rose to 103.6° F. The patient was advised to enter the hospital and was admitted at 5 p.m.

On admission the patient appeared markedly icteric; his temperature was 102° F., pulse 110 per minute and respirations 24 per minute. The sclerae were jaundiced. The only other significant findings were an injected pharynx and a liver edge palpable one finger below the right costal margin. The urine was brown and contained albumin one plus and occasional white cells and granular casts. A blood study at this time (10 p.m.) showed 2,260,000 red blood cells per cubic millimeter with 50 per cent hemoglobin Sahli (7.2 gm.); the total leukocytes numbered 49,300 per cubic millimeter, with 82 neutrophiles, 11 band forms, 4 lymphocytes and 3 monocytes per hundred cells. The smear showed occasional nucleated red blood cells, anisocytosis and some central achromia. The icteric index was 68.0 and the Van den Bergh reaction immediate direct with 6.2 units of serum bilirubin per 100 c.c. of blood. Blood cholesterol was 166.2 mg. with 108.0 mg. per cent (65 per cent of total) as esters. The blood glucose was 97.6, urea nitrogen 24.4, non-protein nitrogen 53.6, uric acid 3.9 and creatinine 1.15 (all in milligrams per cent). The blood Wassermann and Kahn tests were negative.

At 11 p.m. of the day of admission the patient received a transfusion of 500 c.c. of citrated blood. He was placed on a high-carbohydrate diet. His temperature fell to 99.2° F. the next morning and then rose to 100.4° F., remaining at about 100 degrees until the sixth day of hospitalization after which it was normal until the time of discharge.

On April 3, the day after admission, the urine showed albumin 2 plus and occasional red cells, white cells and casts; it was negative for bile but was positive for urobilinogen up to 1:50 dilution. The benzidine test on the urine was 2 plus; spectroscopic examination for hemoglobin was negative. A blood study revealed reticulated erythrocytes 0.2 per cent, 190,000 platelets per cubic millimeter, bleeding time 2 minutes, coagulation time 4 minutes, clot retraction time 6 hours and prothrombin time 100 per cent of normal (Smith's method). An erythrocyte fragility test showed hemolysis to begin at 0.38 per cent and to be complete at 0.30 per cent. The sedimentation rate (Wintrobe method) was 16 millimeters at the end of one hour. The icteric index had fallen to 46.0 and the serum bilirubin to 4.5 units per 100 c.c. of blood; the Van den Bergh reaction remained immediate direct. The bromsulphalein test showed no dye retained in the blood serum after 30 minutes.

Urine examinations on April 4 and 8 showed traces of albumin and occasional casts; two subsequent urine examinations were normal.

On April 4 the red blood cells numbered 2,360,000 per cubic millimeter, with 50 per cent hemoglobin, Sahli (7.2 gm.); the volume index was 0.9 and the morphology of the red blood cells was normal. The total leukocyte count was 14,200 per cubic millimeter, with a differential count of 78 neutrophiles, 3 band forms, 7 lymphocytes, 10 monocytes, 1 young form and 1 eosinophile. The hippuric acid synthesis test showed 1.96 grams of benzoic acid excreted as hippuric acid, indicating impairment of liver function.

The anemia persisted despite active attempts at regeneration as evidenced by a reticulocyte count of 8 per cent on April 5, with red cells 1,980,000 and 42 per cent hemoglobin, Sahli (6 gm.); the white blood cell count then was 12,100 per cubic millimeter. The blood picture remained about the same the next day (April 6), the hemoglobin being 41 per cent, Sahli (5.9 gm.), with 2,020,000 erythrocytes. The sulfanilamide concentration in the blood was determined to be 0.6 mg. per cent.

The jaundice cleared rapidly, the icteric index on April 5 falling to 7.3 while the Van den Bergh reaction was now delayed direct with 0.6 unit of serum bilirubin per 100 c.c. of blood. The stool was negative for blood and bile. Repetition of the bromsulphalein test on April 8 again showed no dye retained in the blood serum after 30 minutes. The blood glucose was 87.8 mg. per cent; the urea nitrogen had decreased to 16.7 mg. per cent; the uric acid was 3.3 mg. per cent and the creatinine 1.23 mg. per cent. The icteric index was only 6.2 and the Van den Bergh reaction again direct delayed with 0.5 unit of serum bilirubin per 100 cubic centimeters.

On April 9 the erythrocytes had increased to 2,920,000, the hemoglobin to 49 per cent, Sahli (7.2 gm.) and reticulocytes to 11.4 per cent. There were 18,800 white blood cells per cubic millimeter, with 58 neutrophiles, 7 band forms, 4 young forms, 2 myelocytes, 17 lymphocytes, 2 eosinophiles, 2 basophiles and 2 Turck cells per hundred cells. The urine at this time was negative for bile and the urobilinogen had fallen to positive in 1:10 dilution. The normal resistance of the red cells to hypotonic saline was confirmed by repetition of the fragility test on April 10, at which time hemolysis was noted to begin at 0.40 per cent and to be completed at 0.28 per cent.

Slow improvement of the blood picture continued. On April 12 the red blood cells numbered 3,360,000 and the leukocyte count was 10,700, with a differential of 68 neutrophiles, 1 band form, 23 lymphocytes, 6 monocytes and 2 eosinophiles. On April 15 the red cell count was the same, the hemoglobin was 68 per cent Sahli (9.9 gm.), and the reticulocyte count had fallen to 1.2 per cent; the leukocyte count was 12,000, with about the same differential.

The hippuric acid synthesis test was performed again on April 17 and showed 2.39 grams of benzoic acid excreted as hippuric acid, indicating an improvement in liver function.

During the remainder of his stay the patient felt better, and visible jaundice disappeared completely April 10. The patient was discharged improved on April 18.

On May 26, five weeks after discharge, the hemoglobin was 92 per cent Sahli (13.3 gm.), the red blood cells 4,310,000 and the white cells 9,850, with a normal differential.

The laboratory findings are summarized in the accompanying chart (chart 2) and graph (figure 1).

Comment

This patient presented many features similar to those of Case 1. There was an early onset of jaundice, following mild gastrointestinal symptoms. This occurred 60 hours after starting sulfanilamide therapy and 24 hours after administration of the drug was discontinued. The total dose given was 110 grains (7.3 gm.). At the same time a moderately severe anemia developed. This was

CHART II

Case 2

	3-31-40	4-2-40			4-3-40	4-4-40	4-5	4-6	4-8	4-9	4-10	4-12	4-15	4-17	5-26
		Noon	10 p.m.	11 p.m.											
BLOOD															
Hemoglobin (Sahli) %	85	55	50			50	42	41		49		66	68		92
Hemoglobin grams	12.3	8.0	7.2			7.2	6.0	5.9		7.2		9.6	9.9		13.3
RBC (millions per cu.mm.)	4.5	3.9	2.26			2.36	1.98	2.02		2.92		3.36	3.36		4.31
WBC per cu.mm.	28,000	20,800	49,300			14,200	12,100			18,800		10,700	12,000		9,850
Neutrophiles per 100 cells	90	76	82			78				58		68	71		60
Band forms per 100 cells	4	2	11			3				7		1	3		
Young forms per 100 cells						1				4					
Myelocytes per 100 cells										2					
Lymphocytes	6	16	4			7				17		23	18		34
Monocytes		6	3			10				6		6	6		4
Reticulocytes					0.2%		8.0%			11.4%			1.2%		
Erythrocyte fragility					0.38 to 0.30						0.40 to 0.28				
Volume index						0.9									
Bleeding time (min.)					2										
Coagulation time (min.)					4										
Icteric index			68.0		46.0		7.3		6.2						
Serum bilirubin units			6.2		4.5		0.6		0.5						
Van den Bergh			Immed. Direct		Immed. Direct		Delayed Direct		Delayed Direct						
Prothrombin time					100%										
Chemistry															
Non-protein nitrogen (mg. %)			53.6												
Urea nitrogen (mg. %)			24.4						16.7						
Uric acid (mg. %)			3.9						3.3						
Cholesterol (mg. %)			166.7												
Cholesterol esters (mg. %)			108.0												
Sulfanilamide conc. (mg. %)							0.6								

Transfusion—500 c.c. Blood

CHART II—*Continued*

	3-31-40	4-2-40			4-3-40	4-4-40	4-5	4-6	4-8	4-9	4-10	4-12	4-15	4-17	5-26
		Noon	10 p.m.	11 p.m.											
URINE															
Appearance			Brown		Reddish Amber	Amber			Straw				Amber		
Urobilinogen (highest positive dilution)					1:50					1:10					
Bile					Neg.										
Albumin			1+		2+	Trace			Trace				Neg.		
Microscopic			Occ. WBC and gran. casts		Occ. RBC and casts	Neg.			Occ. RBC				Neg.		
Spectroscopic for Hgb.					Neg.										
HIPPURIC ACID SYNTHESIS															
Total amount excreted in 5 hours calculated as benzoic acid (gm.)						1.96								2.39	
BROMSULPHALEIN															
Retained in blood after 30 minutes					None				None						

Transfusion—500 c.c. Blood

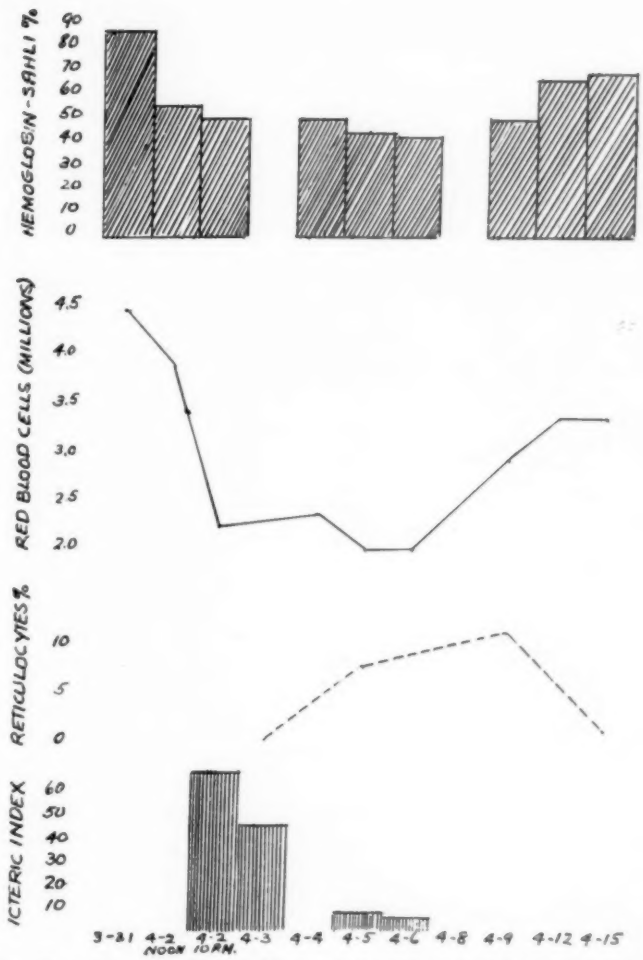

FIG. 1. Case 2. Showing time relationship of fall in hemoglobin and red blood cells to rise in icteric index and reticulocytes.

due to hemolysis of the red cells as shown by the progressive fall in erythrocytes and hemoglobin with marked reticulocytosis. The anemia continued in spite of transfusion, reaching its maximum on April 6, the fourth day of hospitalization. In contrast to the previous case, there was a rise in temperature, a marked leukocytosis, a polynucleosis, and alterations in the morphology of the red cells. Furthermore, there was only a slight response to the transfusion whereas in the first case a dramatic improvement occurred. Evidence of hepatitis (regurgitation jaundice) was present in this case also, as shown by the presence of clinical jaundice, an immediate direct Van den Bergh reaction, increased uribilinogen in the urine, and diminished hippuric acid synthesis, which later improved.

In this case, too, kidney damage was present and was more marked than in the first case. Urinary findings included albumin up to 2 plus, occasional red blood cells and granular casts while blood chemistry studies revealed elevations of urea nitrogen and non-protein nitrogen. Evidence of renal damage disap-

peared one week after admission. The blood picture returned to normal five weeks after discharge and eight weeks after the onset of the illness.

Discussion

There have been described two types of anemia resulting from sulfanilamide therapy, the acute hemolytic and the "slow" or chronic forms. The latter was first described by Jennings and Southwell-Sander.[10] In this type of anemia, the fall of hemoglobin is slow and the maximum is reached in two to four weeks after therapy is started. There is no accompanying bilirubinemia, though increase in the reticulocytes above normal is the rule after the hemoglobin begins to fall. In none of the three cases they presented was icterus present, though in two of them the anemia was quite severe.

The other form, the acute hemolytic anemia, has the following features[3, 11]: (1) A rapidly progressive anemia coming on within three to five days following the onset of drug administration. The hemoglobin, however, begins to fall between 24 and 72 hours after therapy is started. Wood[4] found the anemia to occur only in febrile patients and to reach its maximum between the third and seventh days and usually on the fifth day. The hemoglobin may decline to levels of 30 to 40 per cent of normal during this process. This decline in red blood cells is accompanied by anisocytosis, pallor, many nucleated erythrocytes and reticulocytosis. (2) A polymorphonuclear leukocytosis which varies between 20,000 and 87,000 or more white blood cells per cubic millimeter which on smear exhibit many immature myelocytes. (3) Jaundice and signs of diminished hepatic function in some cases. (4) Prompt recovery following withdrawal of the drug, the use of blood transfusions and forcing fluids to 3000 cubic centimeters a day. (5) A definite rise in temperature during the anemic phase; this manifestation is more common in children than in adults.[12]

Early recognition of the condition may not prevent the progression of the anemia since sulfanilamide may continue to act for as long as 48 hours after its discontinuance. The use of the drug at some later date may cause a recurrence of the acute anemia.

Hepatitis may be mild or severe. The mild cases clear up rapidly after the drug is stopped. The severe cases may go on to acute yellow atrophy and death. As with the anemia, the hepatitis may progress in spite of the discontinuance of the drug, as illustrated by two of the cases presented by Garvin.[7] The symptoms and signs are anorexia, epigastric distress, nausea, at times vomiting, and pain and tenderness in the right upper quadrant of the abdomen, jaundice, enlarged tender liver (in mild cases there may be no enlargement), hyperbilirubinemia, urobilinuria, biluria and decreased hepatic function.

The problem of jaundice is an interesting one. Jaundice may be caused by the destruction of red blood cells, obstruction of the bile passages, or damage to the liver cells by toxic agents or infection. In any given case two or all three factors frequently exist. Skin icterus sets in only 24 hours after the onset of bilirubinemia when the bilirubin reaches a concentration of 1 in 80,000 in the blood. When the blood concentration reaches 1 in 50,000 bile appears in the urine.[13] Hemolytic bilirubin does not pass into the urine unless the concentration becomes very high. Indeed, Van den Bergh[13] and Rich[14] are of the opinion that bilirubin of pure hemolytic jaundice never appears in the urine, the presence of bile in the urine indicating that liver damage has been superadded.

Since the normal liver can excrete more bilirubin than is brought to it, according to Rich,[14] blood destruction per se, with its uncomplicated excess production of bilirubin, is very seldom a cause of jaundice except in rare instances when the hemolytic process is of extreme degree. Excess production of bilirubin, however, is practically always associated with other conditions which tend to impair the excretory power of the liver. Up to a certain point the reserve power of the liver can take care of the excess bilirubin to prevent jaundice. No form of jaundice results purely from a functional depression of the excretory power of the liver, i.e., without actual loss of cells through necrosis. If jaundice does occur from excess bilirubin production, it results from the combination of increased demand upon the liver and decreased excretory power.[14]

Overproduction of bilirubin is ordinarily associated with conditions other than mere overstrain which tend to depress the excretory power of the liver, e.g., anoxemia, etc. It is known that in experimental anoxemia, necrosis of liver cells occurs without a resulting jaundice. If hemoglobin or bilirubin is injected in addition, however, jaundice develops at once.[13] Necrosis or cellular damage reduces the amount of functioning liver tissue and impairs its excretory function. If excess bilirubin is produced, such a liver will be unable to excrete it all and jaundice will result from the retention of excess pigments. It is thus evident that in hemolytic anemias both factors (depressed excretory function due to anoxia and increased production of bilirubin) are present just as in the experimental animal.

When jaundice is noted following drug administration, one must postulate that liver damage or toxic hepatitis is present. Furthermore, Weir [15] has pointed out that hepatitis, even to the extent of fatal acute yellow atrophy, can occur without jaundice. In the 408 cases (101 children and 307 adults) Long et al.[5] studied they found the incidence of jaundice without anemia to be 0.6 per cent, all in adults. If subsequently a hemolytic process supervenes, the drug has extended its activity to the hematopoietic system and the jaundice should deepen because of the increased bilirubin production.

The reason the above facts are being emphasized in this presentation is that in the cases previously reported the presence of jaundice in hemolytic anemias has been ascribed mainly to the hemolytic process and the factor of liver damage has been minimized or overlooked.

The mechanism of injury to the kidney has not been elucidated and the effect on kidney function not determined, and they merit investigation. In this connection it is interesting to note that experimental observation [16] reveals no impairment of renal function by sulfanilamide in therapeutic doses. Ottenberg [9] also experienced some difficulty in attributing the renal damage in his case solely to the sulfanilamide since his patient was receiving milk injections concomitantly. Cases presenting nephritis alone as a toxic manifestation of sulfanilamide would help to settle this problem.

Conclusion

Two cases of toxic hepatitis, acute hemolytic anemia, and renal damage following sulfanilamide therapy have been presented and discussed. Attention has been called to the presence of liver damage in all cases where jaundice is evident.

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ACUTE HEMOLYTIC ANEMIA, HEMOGLOBINURIA AND UREMIA FOLLOWING SULFANILAMIDE*

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While acute hemolytic anemia is a fairly common complication of sulfanilamide therapy and has been carefully studied by numerous workers,[1, 2, 3] massive hemoglobinuria is relatively rare and has received little attention. Among 21 cases of sulfanilamide hemolytic anemia reported by Wood,[3] free hemoglobin was found in the urine in only one instance. Bohlman,[4] in discussing the toxic manifestations of sulfanilamide, referred to a personal communication from Janeway, who had had one case with hemolytic anemia, hemoglobinuria and uremia. In five other cases of sulfanilamide hemolytic anemia, reported in three different papers,[5, 6, 7] hemoglobinuria was noted as an incidental finding, but no mention was made of nitrogen retention.

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It has long been known that massive hemolysis from transfusion of incompatible blood, blackwater fever, etc., results in hemoglobinuria and oliguria and sometimes terminates fatally in uremia. DeGowin, Warner and Randall [8] have reviewed earlier work on the pathogenesis of the renal insufficiency complicating massive hemolysis and have published original studies from which they concluded that the nitrogen retention is due to two factors: (1) tubular obstruction from precipitation of hemoglobin in the loops of Henle; (2) tubular degeneration and necrosis with edema of the interstitial tissue. Finding further that hemoglobin transfused into dogs readily precipitated in the renal tubules if the urine was acid, but remained in solution if the urine was alkaline, they advised prompt alkalinization whenever hemoglobinuria was anticipated or encountered.

To draw attention to the occasional association of massive hemoglobinuria and uremia with sulfanilamide hemolytic anemia, the following case is reported.

Case Report

M. M., a 38-year-old colored male, was admitted to Detroit Receiving Hospital on April 10, 1939, complaining of chills, fever and pain in the chest. For three weeks prior to admission, he had a cough productive of yellowish sputum. On the day of admission he suddenly developed a sharp shooting pain in the right lower chest. Shortly after this he had a severe chill, followed by fever and rusty sputum. Past history was not significant except for pneumonia in 1923. Physical examination revealed a well-developed, well-nourished colored male, moderately dyspneic, and acutely ill. Temperature was 101.6° F., pulse 118, respirations 30. Blood pressure 100 mm. of mercury systolic, 70 mm. diastolic. There was evidence of early consolidation of the right middle and right lower lobes. This was confirmed by roentgen examination. The remainder of the physical examination was negative.

Laboratory: Urine: Specific gravity 1.024; trace of albumin; occasional casts. Blood: Hemoglobin 11 grams; red blood cells 4,330,000; white blood cells 33,000; polymorphonuclear neutrophiles 94 per cent, filamented 18, non-filamented 76 per cent; lymphocytes 6 per cent. Kline test negative. Neufeld examination of sputum revealed type VIII pneumococcus. Blood culture taken on admission was positive for type VIII pneumococcus.

Acute Hemolytic Anemia with Hemoglobinuria. Between 11:00 p.m. on April 10, and 8:00 p.m. on April 13, the patient received a total of 460 grains of sulfanilamide and 415 grains of sodium bicarbonate. On the morning of the twelfth, the blood culture was negative and the temperature, pulse and respirations reached normal. The patient was listless, drowsy and cyanotic at this time but showed no jaundice nor fall in hemoglobin. During the evening of April 12, the temperature rose to 102°, and the next day the urine became dark red in color. Only an occasional red blood cell was discovered on microscopic examination of the urine, whereas large amounts of hemoglobin were found on spectroscopic and chemical analysis. Sulfanilamide was discontinued, whereas sodium bicarbonate was increased to 180 grains and then to 240 grains daily in an attempt to render the urine alkaline. On April 13, the hemoglobin concentration in the blood was 10.0 gm. per 100 c.c. which represented a drop of 1.0 gm. per cent from the admission level. By the following day, the hemoglobin had fallen to 7.0 gm., the red blood count to 1,980,000, and the icterus index had risen to 50. The hemoglobinuria persisted for 24 hours longer, during which time the anemia increased in spite of a transfusion, the red blood count reaching a minimum of 1,650,000 with 5.0 gm. hemoglobin per 100 c.c. on April 15. Methemoglobinemia was detected spectroscopically on April 14 and 15, but disappeared on April 16. The blood fragility to hypotonic saline was normal.

TABLE I

Course

Day	Date	Sulfanilamide grains	$NaHCO_3$ grains	Transfusions c.c.	Fluids		Blood							Urine					
					Intake c.c.	Output c.c.	Hb. G/100 c.c.	RBC	WBC	Ict. Ind.	Sulf. mg. %	Urea mg. %	CO_2 comb. power vol. %	PH	Sp. G.	Alb.	RBC	Free Hb.	Urobilinogen
1	4-10	120	75												1.024	+			
2	4-11	120	120				11.0	4.33	33000		8.6								
3	4-12	120	120				11.5		28000		6.9								
4	4-13	100	120				10.0		31700		8.7				1.010	++++	Occ.		
5	4-14	0	180	350	2810	3700	7.0	1.98	27800	50	5.9	78						+	
6	4-15	0	240	500	3318	2950	5.0	1.65	27900	50	3.9	87			1.010	++++	0	+	0
7	4-16		240	250	2880	700				19	2.0				1.015	+++	0	−	0
8	4-17		240	500	4240	525	5.0	1.93	32100	15	0.9	150	40	7.1	1.015	++	0	−	1–10
9	4-18		240	500	6000	1000	6.0	2.21	28900	13	0.4	117	38	6.9				−	
10	4-19		480		4330	900	6.0	2.16	20500	13	0.4	118	38	6.5	1.008	+	0	−	Tr.
11	4-20		480		6180	900	7.0	2.21	16300	10	0.4	151	31	7.3				−	0
12	4-21		480	500	5050	2200	6.5	2.55	15200		0.7	148	25	6.9	1.008	+	0	−	Tr.
13	4-22		480		4000	2500					0.3			8.9	1.009	+	0		Sl. Tr.
14	4-23		480		3960	2600					0						0		0
15	4-24		480		5930	2340	6.5	2.54	14300		0	107	42	8.3	1.010	+	0		Sl. Tr.
16	4-25		480		6130	2540	6.5	2.30	12900		0	86	40	7.9	1.008	+	Occ.		Tr.
17	4-26		240		3360	2850	6.5	2.43	14500			54	41	7.7	1.008	+	0		0
18	4-27		240	200	3640	2750	6.5	2.77	13100			45	43	8.9	1.012	+	0		0
19	4-28		240	200	5860	2600	6.0	2.15	14650			34	40	9.0	1.012	+	0		
20	4-29		240	200	3360	3200								9.1	1.012	+	0		
21	4-30		240		2140	3000									1.011	0	0		
22	5-1		160	200	3360	3300	8.5	2.97	9650										
23	5-2		160			2600	8.5	3.06	11900						1.010	0	0		
24	5-3		160			2700		3.74											
25	5-4		160	500		3000	8.5	3.68	9900			29	52		1.009	0	0		
26	5-5		80			3000	11.0		12150										
27	5-6		0			2200													
28	5-7		0			2300													
29	5-8					2400						30			1.015	0	0		
31	5-10												42						
33	5-12						11.5	4.27	12450						1.013	0	0		
36	5-15						12.5	5.07	8700						1.013	0	0		
43	5-22						12.5	5.05	12700						1.020	0	0		

Oliguria, Nitrogen Retention. The urinary output was surprisingly good for about 60 hours after the onset of the hemoglobinuria. On April 16, however, the 24 hour output fell to 700 c.c. and on April 17, to 525 c.c. The maximum specific gravity during these two days was 1.015. In the meantime, the physical signs of consolidation disappeared, partial resolution of the pneumonic process being noted in a roentgenogram taken on April 17. From April 18 to April 20, the average daily intake was 5,000 c.c., the average urinary output was below 1,000 c.c. During this period the blood urea remained in the vicinity of 150 mg. per cent. On April 21, the output jumped to 2,200 c.c. and thereafter it ranged between 2,500 and 3,000 c.c. daily. The blood urea gradually fell, reaching 34 mg. per cent on April 28 and remaining normal thereafter. The urinary specific gravity remained low until just before discharge, when it reached 1.020.

Anasarca. Since sodium bicarbonate in a dose of 240 grains daily, together with an alkaline ash diet did not render the urine alkaline, the daily dose was increased to 480 grains on April 19. Three days later, the urine became alkaline and remained so during the administration of soda. On April 19, a small right pleural effusion was found and puffiness of the face was noted. By April 24, the entire right half of the chest was flat to percussion and opaque on roentgen examination. During the next week, 3,650 c.c. of clear straw colored fluid were removed. Although the specific gravity was 1.020 and the albumin content was 26 gm. per liter, the fluid was not inflammatory, as shown by a cell count of 42 lymphocytes and 11 polymorphonuclears per cu. mm. The subcutaneous edema steadily increased, and by April 26, a marked generalized anasarca and moderate ascites were present. Blood pressure at this time was 154 systolic and 90 diastolic. Serum albumin was 3.2 gm. per 100 c.c.; serum globulin 2.1 gm. per 100 c.c. Between April 26 and May 4, the edema steadily diminished in spite of an average daily intake of 200 grains of sodium bicarbonate. Theobromine sodium salicylate was administered in a dose of 60 grains daily during this period but there was no clear cut evidence that it was responsible for the reduction in edema. By May 4, the serum albumin had risen to 4.2 gm. per cent, the globulin to 2.37 gm. per cent.

Result. At discharge, the edema and ascites had disappeared, the lungs were clear, the blood pressure was normal, the urine was negative and the red blood count and hemoglobin were above the admission level. Physical examination on October 17, 1939 revealed no abnormalities. The red blood count was 5,150,000, the hemoglobin 14.5 gm. per 100 c.c. The urine was entirely negative. On urea clearance test, 90.6 c.c. of blood were cleared per minute with a urinary volume of 2.5 c.c. per minute.

Summary

Acute hemolytic anemia with hemoglobinuria, uremia and anasarca developed in a patient who had taken 460 grains of sulfanilamide over a period of 60 hours for the treatment of type VIII pneumococcic pneumonia. A complete recovery was made.

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ACUTE TOXIC NECROSIS OF THE LIVER FOLLOWING THE USE OF SULFANILAMIDE*

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This case is being reported because of the rarity of such severe liver damage following the use of this drug and to emphasize the importance of close observation of every patient receiving sulfanilamide or closely allied drugs.

Case Report

The patient was a white man, 46 years of age. The family and personal past history were without record of value. During the summer of 1938 he had complained of increasing nervousness and the presence of a small lump in the midline of the neck. He consulted his doctor who noted that his pulse varied between 87 and 105. The cardiac rhythm was regular. A basal metabolism test was ordered and reported to be plus 25 per cent. Blood cholesterol was found to be 125 mg. per cent. Urinalysis showed no abnormalities. A blood count showed erythrocytes 4,490,000; leukocytes 7,350; hemoglobin 74 per cent (Newcomer), 12.5 grams. A differential count of the leukocytes showed in each 100 white blood cells: Eosinophiles 1; metamyelocytes II 6; mature neutrophiles 60; lymphocytes 24; monocytes 9.

A clinical diagnosis of toxic adenoma of the thyroid was made and the growth was surgically removed. Histological examination showed a colloid adenoma.

The patient's convalescence was uneventful and he was discharged on the ninth postoperative day. He remained well until September 1, 1939 when he developed gonorrhea. He visited his physician who prescribed sulfanilamide, 30 grains daily, and told him to return in three days. The patient returned complaining that the medicine had made him nauseated. The prescription was changed to 30 grains of Neo-Prontosil daily and he was told to return in three days. He did not return but continued to take the drug in the amount prescribed. During a period of six weeks he consumed 1,250 grains. He then developed malaise and weakness and discontinued the drug. Ten days later he again consulted his physician who noted slight jaundice and ordered a high carbohydrate diet and told him to return the next day. One week later he returned to his physician who noted an increase in the jaundice and the patient was admitted to the hospital for observation. Four hours after admission he became delirious and lapsed into a coma from which he did not recover. The jaundice rapidly increased in intensity; he developed auricular fibrillation and died 36 hours after admission to the hospital.

Physical examination showed the area of liver dullness to be greatly reduced. Over the trunk and extremities were numerous petechial hemorrhages. Blood chemical studies showed: sugar 58.0 mg. per cent; N.P.N. 32.4 mg. per cent; creatinine 1.41 mg. per cent; icterus index 182.8.

* Received for publication January 17, 1940.
From the Department of Pathology, St. Agnes Hospital.

Examination of the blood showed no trace of sulfanilamide. A blood count showed: erythrocytes 5,700,000; leukocytes 13,450; hemoglobin 16.3 gm., 96 per cent (Newcomer).

A differential count of the leukocytes showed in each 100 white blood cells: metamyelocytes II 18; mature neutrophiles 68; lymphocytes 6; monocytes 8.

Summary of Autopsy Findings. Postmortem examination performed by the author revealed a well-developed and well-nourished white male body obviously intensely jaundiced. There were numerous petechial hemorrhages in the skin over the trunk and lower extremities. The pertinent findings on examination of the organs were petechial hemorrhages involving all the serosal surfaces including visceral and

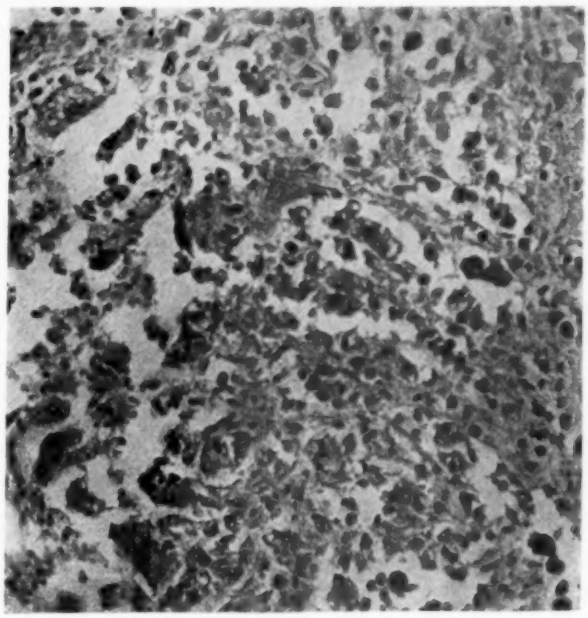

FIG. 1. Section showing necrosis of liver cells. Hematoxylin eosin. × 480.

parietal pleura, pericardium and peritoneum. There was rather extensive subarachnoid hemorrhage involving both parietal areas. The most important finding was marked reduction in size of the liver. It weighed 600 grams. The capsular surface was wrinkled and the organ was flabby in consistence. On section the liver parenchyma presented a mottled appearance with red, yellowish and grayish areas being irregularly distributed. These changes completely obliterated the usual liver pattern. The gall bladder contained thin colorless mucus. The kidneys showed marked cloudy swelling.

Histological examination of the liver showed advanced necrosis of the liver cells. The nuclei had lost the power of staining with basic dyes; the cytoplasm had disintegrated leaving the outline of the cells indefinite. In many areas irregular granular masses and cellular debris were all that remained of the liver cells. The connective tissue structure and masses of necrotic cells were infiltrated by lymphocytes. Sections from many different areas of the liver showed similar lesions.

Discussion

The mode of action of the drug in producing fatal necrosis of the liver is not known. This case serves to further emphasize the importance of close observations on every patient receiving sulfanilamide or any closely allied drugs. This patient complained of nausea following the initial doses of the drug. It would seem advisable to discontinue this type of therapy at the onset of any toxic manifestation, especially in the treatment of such a disease as gonorrhea where the mortality rate is low and other methods of treatment are effective.

EDITORIAL

BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

SINCE the introduction of the Wassermann test in 1906, opinion as to the specificity of serologic tests for syphilis, if reports in the literature reflect the general impressions of the times, has passed through three distinct phases. From 1906 to 1918, many organic diseases, as well as pregnancy, menstruation, and the effect of various drugs, were reported to cause false positive Wassermann tests. In the period 1918 to 1928, these false positive tests were thought to be due to faulty technic or the associated presence of symptomless syphilis, and serologic tests for syphilis were regarded as amazingly specific.

From 1928 to the present, the pendulum is again swinging back. It now becomes clear that many "false positive" tests are due not to technical but to biologic factors.

Two developments have contributed to this reversal of opinion. One is the great increase in the number of serologic tests performed. Because of laws in many states compelling premarital and prenatal serologic tests for syphilis, and their greatly increased routine use in medical practice, many normal persons or those suffering from infections other than syphilis have been found to give biologic false positive tests.

A second and more important factor is the increased sensitivity of modern serologic tests for syphilis. In 1918 Meinicke devised a workable flocculation test which was later improved by Kahn; these original tests of Meinicke and Kahn were less sensitive by 10 to 15 per cent than tests developed after 1928. Hand-in-hand with increased sensitivity came the tendency of these tests to give occasional false positive reactions.

In general, false positive reactions may be of three types. Most frequent are technical false positive reactions due to laboratory errors, which may occur with any type of test. These technical errors are readily recognizable, should cause no confusion in diagnosis and need not be further considered here.

A second category is the biologic false positive tests occasionally encountered in normal persons who have neither syphilis nor any other organic disease. The presence of a reagin-like substance has repeatedly been demonstrated in the serum of many normal animal species other than man. The literature on this subject has recently been exhaustively reviewed by Kemp.[1] The serum of normal human beings has also been thought to contain a sim-

[1] KEMP, J. E., FITZGERALD, E. M., and SHEPHERD, M.: The occurrence of positive serologic tests for syphilis in animals other than man, with a review of the literature, Am. Jr. Syph., Gonor. and Ven. Dis. (In Press.)

ilar reagin-like factor (Dreyer and Walker,[2] Browning,[3] Meinicke[4] and Vernes[5]). Malloy and Kahn,[6] and Barnett, Jones and Kulchar[7] have experimentally demonstrated such a substance in normal serum, but in quantities less than those required to give positive or even doubtful diagnostic tests. Eagle[8] conducted a study of the serologic tests for syphilis on a group of 40,545 white college students. The number of presumably normal persons giving positive tests in the absence of clinical evidence or history of syphilitic infection was small, 1 in 1125 persons tested, and internal evidence suggested that some of these actually had latent syphilis. Nevertheless it seems possible that the serum of an occasional normal person may contain the reagin-like factor in sufficient concentration to give a biologic false positive serologic test for syphilis. It is important that this possibility be kept in mind, particularly in those states in which premarital and prenatal serologic tests are compulsory.

The third and last group of false positive serologic tests are those associated with some organic disease other than syphilis, generally an acute infection. The occurrence of these false positive tests in yaws, leprosy, malaria and infectious mononucleosis has been thoroughly established. Other diseases which have been reported to give false positive tests are: relapsing fever, rat-bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infection, malignancy (particularly carcinoma of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphopathia venereum, chancroid, trypanosomiasis, typhus fever, vaccinia, upper respiratory infections, rheumatic fever, and injections of horse serum. There are also reports to the effect that certain chemicals, when present in the blood stream, will produce false positive tests; ether anesthesia has been incriminated many times in the older literature; acetic acid poisoning and sulfanilamide have recently been suggested as causing false positive tests.

There is no doubt that some and perhaps many of these diseases will actually cause biologic false positive serologic tests for syphilis. A systematic study with respect to the frequency with which false positive tests do occur is urgently needed. It was not until Ester[9] and Kitchen, Webb and Kupper[10] inoculated nonsyphilitic persons with malaria and tested

[2] Dreyer, G., and Walker, E. W. A.: Neues zur Theorie der Wassermannschen Reaktion, Biochem. Ztschr., 1913, liv, 11.

[3] Browning, C. N.: Biochemistry of immune reactions, Brit. Med. Jr., 1915, i, 239.

[4] Meinicke, E.: Theorie und Methodik der serologischen Luesdiagnostik, Deutsch. med. Wchnschr., 1919, xlv, 178.

[5] Vernes, A.: Sur la précipitation d'un colloïde organique par le serum human normal ou syphilitique, Compt. rend. Acad. d. sci., 1918, clxvi, 575.

[6] Malloy, A. M., and Kahn, R. L.: The ultramicroscopic precipitation reaction in syphilis, Jr. Infect. Dis., 1931, xlviii, 243.

[7] Barnett, C. W., Jones, R. B., and Kulchar, G. V.: Measurement of reagin in nonsyphilitic sera, Proc. Soc. Exper. Biol. and Med., 1935, xxxiii, 214.

[8] Eagle, H.: On the specificity of serologic tests for syphilis, as determined by 40,545 tests in a college student population. (In Press.)

[9] Ester, F.: Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, Gior. di batteriol. e immunol., 1936, xvii, 502.

[10] Kitchen, S. F., Webb, E. L., and Kupper, W. H.: The influence of malarial infection on the Wassermann and Kahn reactions, Jr. Am. Med. Assoc., 1939, cxii, 1443.

specimens of blood taken daily from the time of inoculation to several weeks after the temperature became normal that it was realized that not 10 to 15 per cent, as was formerly believed, but a large proportion of the sera (in their series, 90 to 100 per cent) of persons infected with tertian malaria gave biologic false positive tests for syphilis at some time during the course of the infection. A similar approach applied to all the diseases listed above would certainly provide data of clinical significance.

Clarification of the incidence of false positive serologic tests for syphilis in other diseases depends on recognition of the possible transitory nature of biologic false positive tests, and the necessity of repeated tests during the entire course of the disease, continuing well into the convalescent period or until the false reactions have permanently reversed to negative. The application of a quantitative serologic technic to those sera found to be positive should provide data of interest and possible value in the differentiation of biologic false positive tests from those due to actual syphilitic infection.

The complicated nature of the clinical and serologic procedures essential to differentiate biologic false positive tests from those due to syphilitic infection has recently been briefly outlined by Moore [11]; and a new test for this particular purpose (the so-called "verification" test) has just been described by Kahn.[12]

C. F. M.

[11] Moore, J. E.: A suggested method of approach to the recognition of the biologic false positive serologic test for syphilis, Bull. Genitoinfect. Dis., 1940, iii, 1.

[12] Kahn, R. L.: A serologic verification test in the diagnosis of latent syphilis, Arch. Dermat. and Syph., 1940, xli, 817.

REVIEWS

The Patient as a Person. By G. Canby Robinson. 423 pages; 16 × 23.5 cm. The Commonwealth Fund, 41 East 57th St., New York, N. Y. 1939. Price, $3.00.

The author, well known for his career in medical education and in medical investigation, has gone back to fundamentals in medical care through a study of the factors in the illness of 174 unselected patients admitted to the Johns Hopkins Hospital. Illness he defines as "a state in which some of the natural functions of the body are disturbed so that the patient cannot meet the usual requirements of life without pain or discomfort. . . ." In the production of illness it is evident that organic disease is only one factor and that emotional disturbances resulting from various strains and dissatisfactions are often superadded to disease as an element in the illness or in themselves may induce illness.

The patients studied are grouped according to their presenting symptoms, circulatory symptoms, respiratory symptoms, infections, diabetic, etc. They were studied not only as patients in the clinic but as individuals in their home setting.

It will not surprise physicians whose lives have been spent in private practice that the author finds that the outpatient department does not give adequate attention to the rôle of the emotional disturbances in the illness of its patients and that moreover there are serious difficulties in the way of improving this state of affairs. Certain helpful suggestions are offered for the inclusion in outpatient routine of personal conferences of the physician and patient on the background of the latter's illness.

The fundamental difficulty which is not referred to would seem to be that the division of medical care into home care, outpatient care (or office care) and hospital care places the patient under too many different physicians and tends to restrict the interest of the hospital and outpatient physicians to the simpler and more objective factors in the patient's illness to the exclusion of the no less important factors of environment and social relations, which are often quite obvious to the physician who visits the home. The well trained general practitioner who has access to the hospital's diagnostic and therapeutic facilities and to its consultant services is in the best position to assess accurately the nature of the patient's illness and the wisest program of therapy.

M. C. P.

Bacterial Metabolism. By Marjory Stephenson, ScD., Associate of Newham College, Cambridge, Member of the Scientific Staff of the Medical Research Council. 391 pages; 14.5 × 22.5 cm. Longmans, Green and Company, Ltd., London, New York. 1939. Price, $7.50.

This is an enlarged edition of a book which first appeared in the "Monographs of Biochemistry," Series 1930. Owing to the fact that our knowledge of bacterial biochemistry has rapidly increased it was necessary to reproduce it in a larger format.

Following the idea of the first edition it is an attempt to arrange the scattered data in this field in order to appraise our knowledge of the metabolic activities of bacteria. The chapters include respiration, the action of bacteria on polysaccharides and various proteins, protein decomposition products, nitrogen fixation, the metabolism of autotrophic microörganisms, and bacterial photosynthesis. The bibliography is especially complete. This volume is recommended to anyone who is interested in the biochemistry, and metabolism of bacteria.

J. G. Mc.A.

Leukemia and Allied Disorders. By CLAUDE E. FORKNER, M.D. 333 pages; 16 × 24 cm. Macmillan Company, New York. 1938. Price, $5.00.

The author has provided an excellent monograph for the use of the internist. The section on pathologic physiology will be particularly stimulating since much of the information it contains has not heretofore been readily accessible. Likewise there is gathered together under the heading of "Systematic Survey of the Organs and Organ Systems" a very readable account of the ways, both common and rare, in which leukemia may involve all parts of the body. The literature is very fully presented so that more detailed reports on an individual complication become readily accessible.

Later the clinical aspects of the various forms of leukemia are very adequately covered and the leukemoid states described.

The author's attitude in therapy is conservative but most recent and old measures are evaluated. The volume is one which will often be profitably referred to by all students of internal medicine.

M. C. P.

Pneumonia and Its Nursing Care. By HERBERT K. ENSWORTH, B.S., M.D., and LELA GREENWOOD, R.N.; with a foreword by RUSSELL L. CECIL, M.D. 177 pages; 11 × 17.5 cm. J. B. Lippincott Co., Philadelphia. Price, $1.50.

This book, written for nurses, deals briefly with the problem of pneumonia. All points are adequately covered including etiology, pathology, symptoms, various methods of therapy, and nursing care. The authors unfortunately have failed to mention the subcutaneous method of administering sulfapyridine, though the unaccepted new drugs, sulfathiazole and sulfamethylthiazole, have been mentioned. The bibliography divided for each chapter at the end of the book has been well selected. The subject matter is clear-cut and well presented.

This book will prove most useful to graduate nurses who see only an occasional pneumonia case and want a quick review of the subject. Likewise, public health nurses because of their increased responsibility to the indigent pneumonia case, especially in those states with pneumonia control campaigns, will find this small volume helpful.

K. W.

COLLEGE NEWS NOTES

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Books

Dr. Henry Joachim, F.A.C.P., Brooklyn, N. Y., 1940 Edition of "Practical Bedside Diagnosis and Treatment";
Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., autographed copy of "Clinical Diabetes Mellitus and Hyperinsulinism."

Acknowledgment is also made of the receipt of a bound book entitled "Graduate Medical Education," which is a report of the Commission on Graduate Medical Education. Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, is Chairman of the Commission. Other members of the Commission include Dr. James D. Bruce, F.A.C.P., President of the American College of Physicians and Vice President of the University of Michigan; Dr. Anton J. Carlson, F.A.C.P., Hixon Distinguished Service Professor of Physiology of the University of Chicago; Dr. Walter F. Donaldson, F.A.C.P., Secretary of the Medical Society of the State of Pennsylvania; Dr. Reginald Fitz, F.A.C.P., Regent of the American College of Physicians, Assistant to the Dean and Lecturer on the History of Medicine, Harvard University Medical School; and Dr. John B. Youmans, F.A.C.P., Associate Professor of Medicine and Director of Postgraduate Instruction at Vanderbilt University.

Reprints

Dr. Sidney Adler (Associate), Detroit, Mich.—1 reprint;
Dr. Thomas W. Baker, F.A.C.P., Charlotte, N. C.—1 reprint;
Dr. Miles J. Breuer, F.A.C.P., Lincoln, Nebr.—1 reprint;
Dr. Clyde Brooks, F.A.C.P., New Orleans, La.—3 reprints;
Dr. A. David Cloyd (Associate), Omaha, Nebr.—1 reprint;
Dr. George H. Coleman, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Erle B. Craven, Jr., F.A.C.P., Lexington, N. C.—2 reprints;
Dr. Bruce H. Douglas, F.A.C.P., Detroit, Mich.—3 reprints;
Dr. H. R. Edwards, F.A.C.P., New York—3 reprints;
Dr. Edward Gipstein (Associate), New London, Conn.—1 reprint;
Dr. Augustus A. Hall, F.A.C.P., Columbus, Ohio—1 reprint;
Dr. B. R. Heninger, F.A.C.P., New Orleans, La.—1 reprint;
Dr. Leslie R. Kober (Associate), Phoenix, Ariz.—2 reprints;
Dr. Victor W. Logan (Associate), New York—2 reprints;
Dr. John I. Marker, F.A.C.P., Davenport, Iowa—1 reprint;
Major Horace P. Marvin, F.A.C.P., (MC), U. S. Army—1 reprint;
Dr. Thomas H. McGavack, F.A.C.P., New York—6 reprints;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—3 reprints;
Dr. H. Malcolm Read (Associate), York, Pa.—1 reprint;
Dr. Howard A. Rusk, F.A.C.P., St. Louis, Mo.—4 reprints;
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C.—1 reprint;
Dr. Jefferson J. Vorzimer (Associate), New York—1 reprint;
Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.—1 reprint;
Dr. Howard F. West, F.A.C.P., Los Angeles—3 reprints.

The ninety-first annual session of the American Medical Association was held in New York City June 10–14. Dr. Nathan B. Van Etten, F.A.C.P., New York, was inducted as President and Dr. Frank H. Lahey, Boston, was made President-Elect. Aside from the scientific program, action that drew most attention was the creation of a Committee on Preparedness to "establish and maintain contact and suitable relationship with all governmental agencies concerned with the prevention of disease and the care of the sick . . . to make available . . . every facility . . . for the health and safety of the American people and the maintenance of American democracy." The House of Delegates unanimously adopted a report embodying two resolutions, one in the form of a plan for military medical care proposed by the Surgeon General of the U. S. Army, and the other offering the services of the American Medical Association in a national emergency. The specific resolutions follow:

RESOLVED, that the House of Delegates authorize the Board of Trustees to create a Committee on Medical Preparedness, to consist of seven members of this House, with the President of the Association, the Secretary of the Association, the Secretary of the Board of Trustees and the Editor as ex officio members; and be it further

RESOLVED, that this Committee establish and maintain contact and suitable relationship with all governmental agencies concerned with the prevention of disease and care of the sick, in both civil and military aspects, so as to make available at the earliest possible moment every facility that the American Medical Association can offer for the health and safety of the American people and the maintenance of American democracy.

The Committee appointed, to be under the Chairmanship of Dr. Irvin Abell of Louisville, includes Drs. James E. Paullin, F.A.C.P., Atlanta; Stanley H. Osborn, Hartford; Walter G. Phippen, Boston; Harvey B. Stone, Baltimore; Fred W. Rankin, Lexington; Roy W. Fouts, Omaha; Samuel E. Thompson, F.A.C.P., Kerrville, Tex.; Charles A. Dukes, Oakland; and John H. O'Shea, Seattle. Ex officio members are Drs. Nathan B. Van Etten, F.A.C.P., Olin West, Arthur W. Booth, Austin B. Hayden and Morris Fishbein.

The New York session, the first since 1917 in New York City, is said to have had a registration of over twelve thousand, the largest on record.

At the recent annual meeting of the American Gastro-enterological Association, Atlantic City was selected for the next meeting, May 5–6, 1941. The following officers were elected for the coming year: Dr. Andrew C. Ivy, F.A.C.P., Chicago, President; Dr. Russell S. Boles, F.A.C.P., Philadelphia, First Vice President; Dr. Sara M. Jordan, F.A.C.P., Boston, Second Vice President; Dr. Thomas T. Mackie, F.A.C.P., New York, Secretary; Dr. A. H. Aaron, F.A.C.P., Buffalo, Treasurer; and Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., Recorder. Dr. Ernest H. Gaither, F.A.C.P., Baltimore, was elected a member of the Council.

Dr. Laurrie D. Sargent, F.A.C.P., Washington, Pa., as Trustee and Councilor of the Eleventh Councilor District of the Medical Society of the State of Pennsylvania, presided over a meeting of the District at Johnstown, Pa., June 20, 1940. Dr. Belford C. Blaine (Associate), Pottsville, Pa., Chairman of the State Society's Commission on Diabetes, gave a report on the control of diabetes in the State. Reports were received on County Society activities in the District, as well as reports on industrial health and other timely topics.

Western Reserve University recently announced that the John and Mary R. Markle Foundation of New York has made a grant of $2,000 to Western Reserve University School of Medicine to support an investigation of intravenous bismuth

injections, under Dr. Torald Sollmann, F.A.C.P., and Dr. Joseph Seifter of the Department of Pharmacology.

Dr. Ramón M. Suárez, F.A.C.P., San Juan, College Governor for Puerto Rico, has been appointed Head of the Department of Clinical Medicine of the School of Tropical Medicine of the University of Puerto Rico, under the auspices of Columbia University.

Dr. Edward J. Stieglitz, F.A.C.P., Garrett Park, Md., has been made Research Associate in Gerontology at the National Institute of Health. He will organize and develop a new unit of research, to deal with the many problems of aging.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, was recently elected an Honorary Fellow of the Royal Society of Medicine of London, England.

Dr. Lowell S. Selling, F.A.C.P., Detroit, addressed the New York meeting of the American Medical Association, June 14, on "The Mental Hygiene Aspect of the Traffic Accident."

Dr. Selling also addressed the American Psychiatric Association at Cincinnati, May 24, on "The Psychopathology of the Hit-and-Run Driver." He was elected Chairman of the Section on Forensic Psychiatry and has also been elected to the office of Second Vice President of the American Psychopathological Association and a member of the Advisory Editorial Boards of the "Journal of Criminal Law and Criminology" and the "Journal of Criminal Psychopathology."

Dr. Cecil M. Jack, F.A.C.P., Decatur, Ill., has been made an honorary member of the Macon County Tuberculosis and Visiting Nurse Association by the Organization's executive committee.

Dr. D. O. N. Lindberg, F.A.C.P., is Medical Director and Superintendent of the Macon County Tuberculosis Sanatorium.

The Omaha Mid-West Clinical Society will hold its eighth annual assembly October 28–November 1, 1940. Among the guests who will present addresses and clinics are Dr. Samuel Ayres, Jr., F.A.C.P., Los Angeles (Dermatology); Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Dr. Reginald Fitz, F.A.C.P., Boston, Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., and Dr. George R. Herrmann, F.A.C.P., Galveston (Medicine); Dr. Wendell S. Muncie (Associate), Baltimore (Neurology); Dr. Horton R. Casparis, F.A.C.P., Nashville (Pediatrics); and Dr. John T. Murphy, F.A.C.P., Toledo (Radiology).

Dr. Henry T. Smith, F.A.C.P., McGehee, was installed as President of the Arkansas Medical Society at its recent session in Fort Smith.

Dr. Lewis B. Flinn, F.A.C.P., Wilmington, President of the Delaware Academy of Medicine, was toastmaster at a banquet on May 9 to observe the tenth anniversary of the founding of the Academy. Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, was the guest speaker.

Dr. Paul D. White, F.A.C.P., Boston, addressed the Washington (D. C.) Academy of Medicine May 16 on "The Heart in Middle Life."

Dr. Josiah J. Moore, F.A.C.P., Chicago, has been made President of the newly organized Illinois Society of Pathologists. Dr. Israel Davidsohn (Associate) of Chicago was made the Secretary-Treasurer.

Among guest speakers at the annual meeting of the Iowa and Illinois Central District Medical Association at Davenport May 16 were: Dr. August A. Werner, F.A.C.P., St. Louis, "Anterior Pituitary Gonad Relationship in the Female"; Dr. Italo F. Volini, F.A.C.P., Chicago, "A Survey of Heart Disease"; and Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., "How Medicine Began."

Dr. James H. Means, F.A.C.P. and Ex-President of the American College of Physicians, Boston, addressed the Academy of Medicine of Northern New Jersey May 14 on "Some Endocrinopathies for Which We Have Successful Specific Treatment."

Among speakers before a symposium on arteriosclerosis at the Erdmann Auditorium, New York Post-Graduate Medical School and Hospital, June 6, were Dr. Nelson W. Barker, F.A.C.P., Rochester, Minn., "The Conservative Treatment of Arteriosclerosis Obliterans," and Dr. James G. Carr, F.A.C.P., Chicago, "Relation and Importance of Arteriosclerotic Disease in the Heart of Humans."

Dr. Edgar A. Hines, F.A.C.P., Seneca, has been reëlected Secretary for the thirty-first year of the South Carolina Medical Association.

Dr. James G. Carr, F.A.C.P., Chicago, gave the presidential address before the Chicago Society of Internal Medicine May 27, his subject being "The Physician and the Internist."

Announcement has been made that Dr. William deB. MacNider, F.A.C.P., Dean and Kenan Professor of Pharmacology at the University of North Carolina School of Medicine, Chapel Hill, will be awarded the George M. Kober Medal for 1941 for research on the liver and kidneys.

The Montana State Medical Association held its annual meeting at Bozeman, June 19–20, under the Presidency of Dr. Harold W. Gregg, F.A.C.P., Butte.

Dr. Wilburt C. Davison, F.A.C.P., Dean of Duke University School of Medicine, Durham, N. C., gave an address on "Opportunities in the Practice of Medicine" on the occasion of the dedication of new buildings for the Lynchburg (Va.) General Hospital, May 21.

The Canadian Medical Association held its seventy-first annual meeting at Toronto, June 17–21, and was addressed, among others, by Dr. James H. Means, F.A.C.P., Boston, "The Diagnosis and Treatment of Hyperthyroidism," and Dr. Jonathan C. Meakins, F.A.C.P., Montreal, "Shock: Its Recognition and Treatment." Dr. Alan C. Brown, F.A.C.P., Professor of Pediatrics at the University of Toronto Faculty of Medicine, delivered the Blackader Lecture.

Dr. Harry H. Wilson, F.A.C.P., Los Angeles, was installed as President of the California Medical Association at its recent annual meeting in Coronado.

Dr. Buford H. Wardrip (Associate), San Jose, Calif., is President of the newly organized California Trudeau Society.

Dr. William D. Stroud, F.A.C.P., Philadelphia, was one of the guest instructors on the eighth annual postgraduate course of Indiana University School of Medicine, Indianapolis, May 6–11.

Dr. Edward C. Humphrey (Associate), Somerset, Ky., recently resigned as Health Officer of Pulaski County to accept a like position in Mercer County.

Dr. Priscilla White, F.A.C.P., and Dr. Alexander Marble, F.A.C.P., both of Boston, were guest speakers before the Medical Society of the County of Kings, New York, May 21, their subjects being "Diabetes in General and in Relation to Pregnancy" and "Diabetes in Relation to Surgery," respectively.

Dr. Oscar Costa-Mandry, F.A.C.P., San Juan, addressed the Humacao (P. R.) District Medical Society May 5 on "Extension of Laboratory Service in Puerto Rico."

Dr. Rafael Rodriguez Molina, F.A.C.P., San Juan, recently gave an address on "Sprue in the Puerto Rican Indigent" before the School of Tropical Medicine of the University of Puerto Rico.

Dr. Robert B. Hiden (Associate) has been made senior assistant medical director of the Austen Riggs Foundation, Inc., at Stockbridge, Mass.

Dr. Clarence A. Smith, F.A.C.P., Seattle, addressed the Medical Library Association at Portland, Ore., during its forty-second annual meeting, June 25–27, on "Growth, Development and Problems of a Regional Medical Periodical."

The National Research Council, through its division of medical sciences, recently appointed committees to coöperate with the Medical Corps of the U. S. Army and Navy. Among appointees are the following: Dr. Francis G. Blake, F.A.C.P., New Haven, Committee on Chemotherapeutic and Other Agents and Chairman of the Subcommittee on Infectious Diseases; Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Committee on Transfusions.

The Vancouver Medical Association conducted an "annual summer school" at Vancouver June 25–28. Dr. William S. Middleton, F.A.C.P., Madison, Wis., was one of the lecturers.

Dr. George W. McCoy, F.A.C.P., for more than 40 years in the active service of the U. S. Public Health Service, retired on June 30. Dr. McCoy had been Medical Director of Studies on Prevalence and Spread of Leprosy in the U. S. Public Health Service, Professor of Preventive Medicine and Public Health at Louisiana State University Medical Center, New Orleans, Examiner and Member of Basic Science Board and National Board of Medical Examiners, a member of the Council on Pharmacy and Chemistry of the American Medical Association and a member of the U. S. Pharmacopoeia Revision Committee.

He was born at Cumberland Valley, Pa., and graduated from the University of Pennsylvania School of Medicine in 1898. He interned at the City Hospital of Newark, N. J., and joined the U. S. Marine Hospital Service, now the U. S. Public Health Service, in 1900. In 1913 he attained the rank of surgeon in the public health service, and of medical director in 1930. From 1908 to 1911 he was in charge of the Plague Laboratory in San Francisco, and from 1911 to 1915 Director of the Leprosy Investigation Station in Hawaii. From 1915 to 1937 he was detailed as Director of the Hygienic Laboratory, now known as the National Institute of Health, in Washington. From 1922 to 1927 he represented the United States on the Permanent Standards Commission of the Health Section of the League of Nations. In 1931 he was the recipient of the Sedgwick Memorial Medal of the American Public Health Association.

Dr. Harold G. F. Edwards, F.A.C.P., Shreveport, Louisiana, addressed a meeting of the American Radium Society held in New York City June 10 and 11 on "An Analysis of Seven Hundred Cases of Carcinoma of the Cervix."

Dr. Paul F. Dickens, F.A.C.P., Clinical Professor of Medicine at George Washington University School of Medicine, Washington, will have supervision of a research clinic for the treatment of heart disease, as endowed by Homer S. Cummings, LL.D., formerly attorney general of the United States. Mr. Cummings established a fund of $1,200 per annum for five years, to be known as the Cecilia Cummings Research Fund, in honor of his wife who died from heart disease in 1939.

Dr. John R. Williams, F.A.C.P., Rochester, N. Y., was recently awarded the Albert David Kaiser Medal of the Rochester Academy of Science in recognition of "service to the community and to the medical profession." The citation further stated that Dr. Williams "has been the leading spirit, guide and director in the establishment of the Medical Museum in the Rochester Academy of Medicine, which from its beginning has maintained a high standard of educational value for the medical profession and the public. This museum, a new department of academy activity, has already brought into active participation a large number of the medical profession who formerly had no opportunity to take part, as individuals, in the problems of education which face the medical profession."

Dr. Harry V. Paryzek, F.A.C.P., Cleveland, was recently made President-Elect of the Ohio State Medical Association.

Dr. Edward C. Rosenow (Associate), Rochester, Minn., gave an address on "Focal Infections" before the King County (Wash.) Medical Society at Seattle, May 28.

The nineteenth annual convention of the American Physiotherapy Association at New York, June 23–28, was addressed by Dr. Irving S. Wright, F.A.C.P., New York City, on "Pathology of Peripheral Vascular Diseases."

OBITUARIES

DR. DAVID RIESMAN

Dr. David Riesman, aged 73 years, died in the University of Pennsylvania Hospital Monday, June 3, 1940. Members of his immediate family were with him at the end. In his passing, American medicine has lost one of its most distinguished leaders. Dr. Riesman had been ill for several months. An autopsy revealed a small carcinomatous growth in the lower bowel with generalized metastasis.

Dr. Riesman was born March 25, 1867, near Eisenach in Saxe-Weimar, Germany. In his boyhood, he was brought to Portsmouth, Ohio, where he was graduated from the public high school. He entered the University of Michigan in 1889, but after a course of one year he came to the University of Pennsylvania School of Medicine in 1890 and graduated in 1892, following which he became an instructor of pathology at the University and began his internship at Philadelphia General Hospital, where he continued to serve throughout his lifetime as pathologist, visiting physician and president of the medical board.

In 1900 he became instructor of clinical medicine in the University and in 1912 succeeded the late Dr. John H. Musser to the professorship until 1933, when he retired from routine teaching. At the time he was stricken, his weekly routine included two lectures at the University, consultations at seven hospitals along with the conduction of an ever-growing practice.

Dr. Riesman was consultant to the University of Pennsylvania Hospital, Philadelphia General, Women's College, Jewish, Chestnut Hill, Kensington and Graduate Hospitals. During a visiting lecture series at Harvard University in 1927, he was physician-in-chief of Brigham Hospital, Boston.

A host of societies claimed his active membership. Among those of which he had been president are: Philadelphia County Medical Society, Philadelphia Pathological Society, American Society of Medical History, Northern Medical Association, Interstate Postgraduate Medical Assembly of North America, Inter-Urban Clinical Club, Philadelphia Heart Association, and the American Gastro-enterologic Association.

Dr. Riesman was also a member of the Philadelphia College of Physicians, Medical Society of the State of Pennsylvania (formerly chairman of the Section on the Practice of Medicine), American Medical Association, American Association for the Advancement of Science, Medieval Academy of America, French Prehistoric Society, British Philosophical Association, American Board of Internal Medicine (Adviser and Diplomate), American College of Physicians (Fellow since January 1, 1921), History of Science Society, Foreign Policy Association, University Club, Franklin Inn Club and numerous other Philadelphia Societies, including Neurological, and Pediatric societies.

Among his many other talents, Dr. Riesman was author of a long host of publications, including the following: "American Textbook of Pathology (with Ludvig Hektoen)," 1901, W. B. Saunders; "Thomas Sydenham," 1925, Paul B. Hoeber; "The Story of Medicine in the Middle Ages," 1935, Paul B. Hoeber; "Medicine in Modern Society," 1938, Princeton University Press. One of his later publications was the "History of the Medical School of the University of Pennsylvania," appearing in the "Scope," University of Pennsylvania Class of 1939. He also wrote innumerable articles for medical journals.

To the Doctorate of Medicine, which he received in 1892, were added an honorary Doctor of Science degree by Franklin and Marshall College and Doctor of Laws degree by the University of Wisconsin. He was to receive another honorary doctorate from the University of Pennsylvania at its commencement exercises June 12, 1940. He was awarded the I. P. Strittmatter medal for 1928 by the County Medical Society for "service redounding to the credit of the profession." President Clarence A. Dykstra, of the University of Wisconsin, conferred the legal degree on Dr. Riesman in 1937 as "the statesman of medicine."

Dr. Riesman was married January 20, 1908, to Eleanor L. Fleisher, a brilliant woman to whom he always directed credit for his vast mental breadth. Besides his wife, Dr. Riesman leaves two son, John Penrose Riesman, now an intern at Philadelphia General Hospital, and David, Jr., professor of law at the University of Buffalo, and a daughter, Miss Mary Riesman, who is a New York City school teacher.

By the death of David Riesman, The American College of Physicians has lost one of its great and loyal members.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

MAJOR GENERAL JOHN TAYLOR FOTHERINGHAM

In the loss of Major General John Taylor Fotheringham, F.A.C.P., Toronto, the medical profession of Canada has lost a very distinguished member.

Dr. Fotheringham became a Fellow of the American College of Physicians in 1922 and during his active career he was a member of every organization that has stood for the advancement of the profession. He was one of the fathers of the Canadian Army Medical Corps, in which he was promoted to the rank of Major General.

Dr. Fotheringham had been in poor health for some time, but he had evinced keen interest in the developments of the present war. He was honored with a full military funeral from St. Andrew's Presbyterian Church.

Recognized for his outstanding gifts as a teacher, Dr. Fotheringham served for some years on the medical faculty of Trinity Medical School and later the University of Toronto. He was a valued member of the medical

staff and consultant of the Toronto General Hospital and Hospital for Sick Children. He won many honors during his distinguished military career and served continuously during the last war with the Canadian Army Medical Corps. He had been with the corps since its inception in 1900.

Born at Kirkton, Perth County, Dr. Fotheringham was the son of the late Rev. John and Helen Telfer Fotheringham. He received his early education at St. Mary's Collegiate Institute. Graduating in 1883 from University College, Toronto, with first-class honors in classics, he devoted several years to teaching and at one time was classics master at Upper Canada College. He graduated from Trinity Medical College in 1891 as a silver medalist and at the same time received the degree of M.B. from the University of Toronto.

Enlisting with "K" Company, Queen's Own Rifles, in 1879, he was appointed surgeon-lieutenant of the 12th Rangers in 1896. A year later he was transferred to the Queen's Own Rifles with the same rank.

At the outbreak of the last war in 1914 he enlisted for active service and was raised to the rank of colonel. He was appointed assistant director of medical services for Military District No. 2 and served overseas with the Second Canadian Division. In 1917 he was recalled from France to reorganize army medical services and was made director-general of military medical services for Canada, which office he held until 1920. On his return to Ottawa he was made a Major General.

He was awarded the C.M.G. while in France and was mentioned in dispatches several times. In 1924 he was gazetted honorary colonel of the Royal Canadian Army Medical Corps.

His academic career was equally brilliant and in 1892 he was appointed to the staff of Trinity Medical School as lecturer in therapeutics and clinical medicine. Following the amalgamation of Trinity Medical School with the University of Toronto he continued on the staff as assistant professor in clinical medicine. Dr. Fotheringham was the first incumbent of the chair established in 1924 by the University of Toronto in history of medicine. In 1918 he received the honorary degree of LL.D. from both the University of Toronto and from Queen's University. He was also created a Knight of Grace, the Order of St. John of Jerusalem. From 1919 to 1922 he was honorary surgeon to the Governor General of Canada at Ottawa.

As a physician he had served on the staff of St. Michael's Hospital, the Hospital for Sick Children and with the Toronto General Hospital. He was in charge of the outpatients' department, St. John's Hospital, from 1920 to 1930.

Dr. Fotheringham was a life member and past president of the Canadian Military Institute, honorary life member and past president of the Academy of Medicine, member of St. Andrew's Society, the Corporation of Trinity College, the senate of the University of Toronto, Board of Management of Knox College, life member of the Canadian Medical Association and St. Andrew's Presbyterian Church. He was honorary consultant physician for

both the Toronto General Hospital and Christie Street Military Hospital, and was consulting physician-in-chief for St. John's Medical Mission.

Dr. Fotheringham was married in 1891 to C. Jennie McGillivray, daughter of George McGillivray, who predeceased him. Surviving him are two daughters, Miss Helen, at home, Mrs. Ruth Kilpatrick, and one son, Donald T. Fotheringham.

"General Fotheringham's death marks the passing of one of Canada's most distinguished physicians and soldiers," said Major General John A. Gunn. "He was a great character and a marvelous lecturer. Throughout his life his service to mankind and his beloved Canada was his chief thought. Fortunate indeed were those who were privileged to come under his influence and to be regarded as his friends."

J. H. Holbrook, M.D., F.A.C.P.,
Governor, Province of Ontario

CAPTAIN CARROLL R. BAKER

Captain Carroll R. Baker, F.A.C.P., Medical Corps, U. S. Navy, died at the U. S. Naval Hospital, Washington, D. C., on April 23, 1940. Captain Baker was born at Winchester, Virginia, on April 1, 1885. He was a graduate of Jefferson Medical College, class of 1909 and served his internship at the Philadelphia General Hospital from 1910–11. He received a certificate of graduation from the U. S. Army Medical School in 1912.

Dr. Baker was commissioned an assistant surgeon in the Medical Corps of the Navy on April 10, 1914 and graduated from the U. S. Naval Medical School that year. He was promoted to the rank of lieutenant on August 29, 1916; to the rank of lieutenant commander on March 4, 1921; to the rank of commander on August 28, 1926; and to the rank of captain on February 1, 1937.

During his service in the Medical Corps of the Navy, Dr. Baker was on duty at various naval activities. He specialized in internal medicine and was an authoritative consultant in the field of cardiology. During his service career, he undertook numerous postgraduate courses in his chosen field. He served as executive officer of the Naval Medical School, Washington, D. C., from August, 1928, to July, 1931; chief of medicine on board the U. S. S. *Relief* from July, 1931, to June, 1933; chief of medicine at the Norfolk Naval Hospital, Portsmouth, Virginia, from June, 1933, to June, 1936; executive officer at the Naval Dispensary, Navy Department, Washington, D. C., from June, 1936, to March, 1937; personnel officer in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., from March, 1937, to October, 1938. At the time of his death, he was serving as chief of medicine at the Naval Hospital, Washington, D. C.

Ross T. McIntire, M.D., F.A.C.P.,
Governor for the U. S. Navy

DR. JAMES WILSON HUNTER

Dr. James Wilson Hunter, F.A.C.P., of Norfolk, Virginia, died on May 11, 1940, of coronary occlusion, at the Army and Navy General Hospital, Hot Springs National Park, Arkansas. Dr. Hunter was born in Norfolk, Virginia, April 30, 1878. He received both his A.B. and M.A. Degrees from the University of Virginia in 1889 and his M.D. Degree from the Department of Medicine of that institution in 1901. For many years he was active in the field of roentgenology and a member of staff of the Hospital of St. Vincent de Paul, Norfolk General Hospital and Leigh Memorial Hospital. He served in the World War with the rank of Captain in the Medical Corps of the U. S. Army. He was a member and a former president of the Norfolk County Medical Society and a Fellow and Life Member of the American College of Physicians. He also held membership in the American College of Radiology, American Heart Association, American Medical Association, Virginia State Medical Society, and numerous other scientific bodies.

WALTER B. MARTIN, M.D., F.A.C.P.,
Governor for Virginia

RECENT ANNOUNCEMENTS

Program of Postgraduate Courses under Consideration

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Chairman of the Governors' Advisory Committee on Postgraduate Courses, in conjunction with the Regents' Committee on Educational Policy, held a meeting in New York City, June 12, for the discussion of policies, courses and dates for the schedule of Postgraduate Courses to be offered by the College during the coming year. Those present included Dr. Bortz as Chairman, Dr. Ernest E. Irons, Chicago, Dr. C. Sidney Burwell, Boston, Dr. Fred M. Smith, Iowa City, Dr. James E. Paullin, Atlanta, and Mr. E. R. Loveland, Executive Secretary of the College.

Used as a guide were the reports which had been collected from the Director of each Postgraduate Course and each registrant for the past year. Especially valuable were the suggestions of members of the College who have pursued these Courses.

The Committee is extending its study by sending a questionnaire to every Fellow and Associate of the College. In addition, it is requesting each Officer and Regent to offer recommendations for the further development of the Postgraduate Courses. As soon as the Committee has had ample opportunity to study carefully the reports from the course organizers, students who have taken the courses and the statements from the members of the College and recommendations of the College Officers, the Committee will present its final report to the Board of Regents. Thus far, many constructive comments have been received. The student doctors who have attended these courses given by the College, since their inception, have sent in most enthusiastic letters to the Executive Offices of the College. There is a rapidly growing interest and demand for Postgraduate Instruction in Internal Medicine, and it is the consensus of opinion that the American College of Physicians should display energetic leadership in this important field. It might be advisable to offer courses varying from one, two or four weeks in length; some to be offered in the autumn, others in midwinter and finally a certain number to be presented just antedating the Annual Session of the College.

There is a growing demand for courses two to four weeks in length in advanced general medicine. The most popular request, however, is for instruction in special fields such as Cardiology, Hematology, Gastro-enterology, Psychiatry, Neurology, etc. It may be that a combination course with two weeks in advanced medicine together with one or two weeks of instruction in a special field would prove attractive.

While these courses were created originally, solely for the members of the College, several men on the Committee have signified their interest in admitting to the courses qualified non-members of the American College, who are recommended by an Officer, Regent or Governor of the College. With the admission of carefully selected non-members, the College would, by this movement, assist men aspiring to Fellowship in the American College to attain advanced training in Internal Medicine.

If the American College of Physicians offers Postgraduate Courses at different seasons of the year, it may be possible for men to take more than one course per year. Coördination of the courses offered should be of such a nature that, over a period of three or four years, the student who desires may receive the equivalent of a year's study in advanced Internal Medicine, ordinarily leading to some degree.

There was a consensus of opinion that the College has been primarily instrumental in setting up the advanced requirements for the practice of Internal Medicine, not only through its own standards of admission, but through the examinations of the American Board of Internal Medicine, and that, therefore, the College has an obligation to see that facilities shall be available to enable men to meet such advanced

requirements. The program will be further developed and announced in the early autumn.

Bailey K. Ashford Award in Tropical Medicine Established

In honor of the late Dr. Bailey K. Ashford, F.A.C.P., Eli Lilly & Co. established the Bailey K. Ashford Award in Tropical Medicine during the last annual meeting of the American Society of Tropical Medicine in Memphis. The Award will be made on alternate years for a total of three years and will consist of $1,000 in cash, an engraved bronze medal and an additional amount of $150, or as much thereof as may be required, toward traveling expenses for the recipient. The Award will be made " in recognition of demonstrated research in the field of tropical medicine, taking into consideration independence of thought and originality." The investigator must be a citizen of the United States of America and less than thirty-five years of age. He must not be associated with a commercial laboratory and need not be a member of the American Society of Tropical Medicine. Members of the American Society of Tropical Medicine may submit nominations to the Secretary of the Society in triplicate, with full information concerning the candidate's personality, training and research work. Nominations must be submitted sixty days before the annual meeting, at which the Award is to be made. The recipient will present a review of his work at the meeting.

Summary of the Report by the Commission on Graduate Education

Important developments in the hospital internship, the hospital residency and the postgraduate educational opportunities for physicians in practice were suggested by the Commission on Graduate Medical Education, whose final report was published on June 25. The Commission, which was organized by the Advisory Board for Medical Specialties on December 4, 1937, is now bringing to a close its three year study program. Its work has been financed by national foundations and interested professional organizations.

The internship, suggests the Commission, should be considered as a basic preparation for the practice of medicine. It should round out and give practical application to the medical school course and, hence, should be closely allied to undergraduate medical education. It should prepare young physicians adequately to begin general family practice and should provide them with the essential preparation necessary to undertake further study leading to the practice of a specialty. It should not attempt to train men for the specialties directly and, therefore, the intern should not be given training in the detailed technics of the specialties.

To prepare the intern for general practice, he should have experience in internal medicine, pediatrics, obstetrics and gynecology, and surgical diagnosis, minor surgery and treatment of emergencies. Special attention in these fields should be given to preventive medicine and the care of chronic diseases, conditions of the aged and functional disturbances. The whole atmosphere should be educational in character and he should learn by example as well as precept.

The residency is defined by the Commission as a prolonged period of study in one of the special fields which can be properly classed as graduate education, whether an advanced degree is granted or not. The Commission warmly supports the recommendation of the speciaity boards that adequate attention be given during the residency to the basic sciences as they relate to the various specialties. It suggests practical ways by which hospitals may provide this basic science training in their own laboratories or through arrangements with medical schools. The report suggests that there is danger that too many residencies may be developed and stresses that, in the best interests of the patient, high quality of teaching in the residency is now

more important than a large increase in the number of residencies. The essentials of a satisfactory residency are listed in some detail, although the Commission takes pains to point out that it does not wish to standardize residencies or put them in a strait jacket.

Postgraduate education the Commission defines as study intended to keep a physician abreast of his chosen field of practice but not intended to equip him to enter a new field. Separate and clearly defined types of work are recommended for general practitioners and for specialists. While there has been a marked and rapid increase in interest in the field of postgraduate medical education, there is still need for its further extension and for improvement in the type of opportunities offered. The report points out the advantages and disadvantages of the various types of training now provided.

The effect of the work of the specialty boards upon the practice of medicine is discussed in the report, which points out that these boards have provided a well defined yardstick for measuring an individual physician's competence in his specialty. Men in the specialties have been certified so rapidly that it soon will be possible for the great majority of the people of this country to have access to the services of certified specialists.

The entire report stresses the value of adequate training and points out that this will be reflected in improved care of patients.

MINUTES OF THE BOARD OF REGENTS

SECOND MEETING, APRIL 2, 1940

The second meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, took place at the Cleveland Public Auditorium, Cleveland, Ohio, April 2, 1940, with President O. H. Perry Pepper presiding, with twenty-two members of the Board present and with Mr. E. R. Loveland acting as Secretary.

Secretary Loveland gave a short summary of the Minutes of the preceding meeting of the Board, which was approved as read.

Among communications were:

(1) A report from Dr. Charles H. Cocke, Chairman of the Board of Governors, concerning the transactions of the first meeting of that Board.

(2) A telegram from Dr. Frank J. Sladen, Director of the Postgraduate Course, "Medicine in Industry," sponsored by the College at Detroit, in which Dr. Sladen expressed his appreciation, inspiration and enthusiasm.

Dr. William J. Kerr inquired if there had been any provision for assembling notes on that particular Course for publication, feeling that the topics were of very great interest and might be of value to everyone in the College.

It was reported that the expense attached to recording these Postgraduate Courses was so great that no attempt had been made to do so.

Dr. Kerr further suggested that if any notes are available, it might be desirable to mimeograph them, or to arrange them in more permanent form for distribution, after Dr. Sladen had been consulted.

(3) A telegram from Dr. James B. Herrick, acknowledging and expressing his appreciation of the honor of being made a Master of the College. The Secretary was instructed to reserve a room at the Headquarters' Hotel for Dr. Herrick's use on the occasion of the Convocation.

Unfinished Business from Preceding Meeting

The following report was received from the Treasurer, in absentia, because of his having to conduct one of the Panel Discussions on the program:

"As of March 28, 1940, the book value of our Endowment Fund in bonds is $78,452.50 and in stocks, $13,650.00, totalling in the Endowment Fund, $92,102.50.

"In the General Fund, we have in stocks invested $82,245.00, making a total book value of our investments as of that date, $174,347.50, which makes an increase in the total book value of our invested funds during the past year of $2,215.22.

"Our securities have averaged an interest on investment of 4 per cent during the past year. Our operating balance of net income over expenses is $23,939.07.

"I feel safe in reporting to you that the finances of our College are in a sound condition.

Respectfully submitted,

WILLIAM D. STROUD,
Treasurer"

On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that the report of the Treasurer be accepted and filed.

The Executive Secretary, Mr. Loveland, distributed mimeographed copies of the financial report for 1939 and copies of the consolidated budgets for 1940.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported as follows:

"At the last meeting of the Board of Regents, December, 1939, the Board of Regents appointed five Research Fellows for 1940–41. Among them was Dr. Richard Lyons, who has informed the Committee that he would be unable to accept the fellowship because of another opportunity. Apologetic letters had been received from his sponsors at the University of Michigan, who apparently felt that this other opportunity was so good that Dr. Lyons was justified in taking it. Other members of the Committee had been circularized concerning the appointment of another Research Fellow in Dr. Lyons' place. Other applicants, in the opinion of the Committee members, were not of such caliber to justify their appointment. Soon thereafter word was received from Dr. Hugh J. Morgan, of Nashville, Tenn., concerning Dr. Homer Swanson, who has been working at Vanderbilt University, but whose arrangements could not be carried out further without a fellowship grant. Dr. Morgan was invited to present to the Committee Dr. Swanson's qualifications as a possible Research Fellow, and the Committee at this time request Dr. Morgan to present the candidate's qualifications to the Board of Regents."

Dr. Hugh J. Morgan presented all salient details concerning the preparation, interest, qualifications and history of the candidate.

On motion by Dr. Barr, seconded by Dr. William J. Kerr, and after general discussion of the candidate's age, date of graduation and other qualifications, the following resolution was unanimously adopted:

RESOLVED, that Dr. Homer Swanson shall be awarded a Research Fellowship of the American College of Physicians in the amount of $1,800.00 for a period of one year, beginning July 1, 1940.

It was thereafter pointed out that this was the first occasion on which the College had awarded a Research Fellowship in Neurology, an act that met with general approval.

The Committee on Fellowships and Awards presented adverse recommendation in regard to a request for a subsidy of $150.00 for work contemplated in Hematology at the University of Louisville, based upon the fact that the College had adopted no policy concerning subsidies and that the Committee believed that in this instance a subsidy might be obtained from the Council on Pharmacy and Chemistry, or through another source of the American Medical Association or elsewhere.

The matter was generally discussed, and there appeared to be no definite feeling that the College should embark on the subsidizing of individual research.

Dr. Ernest B. Bradley raised the question as to whether the Committee had ever considered whether all Research Fellows require as much as $1,800.00 for their year's work?

Dr. Francis G. Blake stated that in the National Research Council funds are somewhat more liberal in amount, the minimum being $1,800.00. Since less funds have been available, after careful investigation, the Council has given some awards of not more than $1,600.00 for a single man in communities in which it was felt that he could get along adequately on that amount; $2,300.00 for a married man; with $200.00 more added for children. Dr. Blake felt that in many instances, $1,600.00 has proved quite adequate for younger men.

Dr. David P. Barr pointed out that the regulations of the College Committee on making awards provide that the man must be accepted by the institution in which he wishes to work, and that the institution agrees to supply such things as are necessary for the conduct of the work.

On motion by Dr. Robert A. Cooke, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, that the report of the Committee on Fellowships and Awards be accepted.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented a report dealing with resignations, waiver of dues, communications concerning various matters of public relations.

On motion by Dr. Paullin, regularly seconded and adopted, the resignation of one Fellow was accepted, the dues of three Associates and one Fellow were temporarily waived because of illness, the dues of one Fellow were deferred because of an accident, the request for the waiver of dues in one instance was refused, and the endorsement of the American College of Physicians was given to the American Foundation of Tropical Medicine.

Dr. Sydney R. Miller presented the revised informative booklet in proof form, and a resolution was adopted that after additional revisions had been made the proof be re-distributed to all members of the Board of Regents before being finally published.

Dr. Walter W. Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported a meeting of that Committee on April 1. Two matters under consideration, presented by the Editor, were the size of the volume of the ANNALS per year and the matter of the Rheumatism Review. It was the opinion of the Committee that the budget more than amply covers the publication of 2,400 pages of scientific material per year, and it was the consensus of opinion of the Committee that the ANNALS should not exceed this size, but could properly go up to that limit. In regard to the Rheumatism Review, it was pointed out that this year the Review is a long one, covering some two hundred pages which, in the opinion of the Committee, is in excess of the importance of the subject, although an admirable Review had been submitted. The Committee recommended that in the future the Review, if submitted to the ANNALS, should not exceed one hundred pages, and preferably should be under one hundred pages. Dr. Palmer added that the Committee had only admiration for the manner in which Editor Pincoffs has handled the ANNALS, and that the Journal has improved consistently in a most desirable manner.

EDITOR PINCOFFS: "To exculpate the Rheumatism Review, I might say that they themselves have written me concerning the fact that they had exceeded the proper length of this Review and were quite willing to cut it down, and asked the opinion of the Editor as to the size that it might properly be, if we wish to continue to publish it. Your Editor is very glad to have the action of the Committee on the ANNALS, and he will write them, suggesting that it be held to one hundred pages."

In answer to an inquiry from President Pepper concerning the limitation of the volume in size, Editor Pincoffs expressed his approval of the limitation suggested for the time being, but not as a permanent rule, asking that the matter be passed upon in such a way that it might be subject to some change of action on the part of the Regents later. The question of publishing the Rheumatism Review as a supplement to the ANNALS was discussed, and the Editor pointed out the disadvantages in cost and distribution that made such procedure inadvisable. The cost of publishing the current Rheumatism Review as a supplement was found to be about twelve hundred to fifteen hundred dollars, plus the additional cost of distribution. The Finance Committee had declined to approve of this expenditure.

Dr. James E. Paullin inquired why the American Rheumatism Association might not be willing to contribute something toward the publication of this Review. Editor Pincoffs said he was unacquainted with that Association's financial status, but in the original negotiations of their representatives on the publication of this Review, that Association had asked whether the College would be interested in the publication

simply as a Review in the ANNALS, stating that its committee felt they had no funds otherwise to publish it and were offering it to the College first. Dr. Pincoffs expressed the opinion that if the Review is cut down to one hundred pages, it is just as worthy for free publication in the ANNALS as any other material. This particular article, or review, has led to more calls from outsiders for copies of the ANNALS than any other article. Dr. Pincoffs also stated that the Archives of Internal Medicine not only publish some reviews free, but pay the men who make the reviews.

In the discussion that followed, it was brought out that the authors of the Rheumatism Review have the College printers run off several additional copies bound as a single publication, and that they distribute them to the members of their Association and also have them for sale. In this way the authors are saved the expense of typesetting and can secure copies at very reduced rates. If these are put on sale they naturally can be distributed at considerably less cost than can the College distribute copies of the ANNALS itself in which the Reviews appear.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Ernest B. Bradley, and regularly carried, it was

RESOLVED, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be accepted.

President Pepper called upon the Chairman of the American Board of Internal Medicine for a report.

DR. ERNEST E. IRONS: "The American Board has now issued 2,158 certificates. Of these, 358 were certified by examination. In addition, 111 candidates were examined on Saturday and Sunday last. A brief review of the four years' work of the Board was presented yesterday. Our finances are in a healthy condition. Our bank balance was $18,548.14 on January 1, 1940. We have no financial obligations outstanding. Negotiations are proceeding satisfactorily in the matter of providing for recognition of medical sub-specialties in the work of the Board. A cordial working arrangement between the College, as represented by the Committee on Graduate Medical Education under Dr. Morgan, the Council on Medical Education of the American Medical Association, and the Board of Internal Medicine has been worked out and is in operation."

President Pepper called for a continuation report from the Committee on Postgraduate Education:

DR. HUGH J. MORGAN: "I wish to withdraw certain suggestions which were made at our preceding meeting relative to the reorganization of the Postgraduate Committee of the Regents. I would like you to consider the advisability of delegating the authority in this meeting to such worthy representatives of the College who are to participate in the work of the Conference Committee of the Council on Medical Education and Hospitals, and that representatives of the College may be appointed, perhaps, outside of the Board of Regents. I think there may well be two men in the College—Regents, Governors or Fellows—who could represent the College and do a much better job on this Conference Committee than I will be able to do. I don't want to go on this Conference Committee as a rubber stamp for the Council, and I am afraid that is what will happen, unless we get representatives on that Committee who are interested and who have the time to put in a lot of solid work. I hope it can be made possible for the College to be represented by someone other than the Chairman of the Postgraduate Committee on this Conference Committee."

PRESIDENT PEPPER: "The matter brought up by Dr. Morgan is entirely within the authority of the Regents. The Postgraduate Committee is a creature of this Board, and the appointments to the Conference Committee were not ex officio, but

were simply by the President in his wisdom. It is quite within the power of this Board to state that these appointees to the Conference Committee and the Committee on Postgraduate Education itself may be drawn from the Regents, the Governors, or the membership at large, and then the matter may be left to the incoming President's duty to makes these appointments."

On motion by Dr. Hugh J. Morgan, seconded by Dr. James D. Bruce, and carried, it was

RESOLVED, that appointments from the American College of Physicians to the Conference Committee on Graduate Training in Medicine be left to the incoming President, Dr. James D. Bruce, who may appoint men to these positions from the College at large, including the Governors.

Dr. Ernest E. Irons, speaking to the motion, said that Dr. Morgan had done an exceptional job thus far, and it should be hoped that the incoming President would be able to convince Dr. Morgan, in spite of his moral responsibility to his school, to continue on that Committee, and that the College needs Dr. Morgan's supervision and drive to carry through the College plans.

Dr. James D. Bruce also complimented Dr. Morgan's work, and expressed the hope that he would agree to continue to serve.

President Pepper reiterated Dr. Irons' sentiments, commending Dr. Morgan's efficiency and skill on this Committee.

Dr. Morgan then was asked to re-present the suggestion concerning a formal certificate of attendance for the Postgraduate Courses.

On recommendation and motion by Dr. Hugh J. Morgan, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, that the College, through its Executive Offices, shall issue to each physician attending its postgraduate Courses a formal card attesting to his having enrolled and attended a specific Postgraduate Course sponsored by the College.

Furthermore, it was agreed that this card could be presented by Associates as a helpful credential when said Associates are qualifying for advancement to Fellowship. It was also directed that this card be sent to all men who have taken the Courses in the past, as well as for the current year.

Dr. Morgan again brought up the matter of the policy of the College relative to research and clinical fellowships. He suggested that the Regents should first decide how much of the College funds shall be put into fellowships each year, and then determine how much shall be segregated to research fellowships and how much to clinical fellowships. He felt that the present Research Fellowships have been extended from year to year somewhat haphazardly without actually confining the limit of the amount of money to be spent. He emphasized the need of fellowships for training of men to go into practice, to extend the number of opportunities that there are in the country for what actually amounts to residency experience in Internal Medicine.

President Pepper recommended that the incoming Committee on Fellowships and Awards and the incoming Committee on Finance should be asked to consider this recommendation before the preparation of the budget for 1941.

On motion by Dr. James D. Bruce, seconded by Dr. Sydney R. Miller, and carried, it was

RESOLVED, that the President be instructed to send a telegram to the Surgeon Generals of the Army and Navy, thanking them for having assigned Officers from their respective Services to give the Symposium on Military Medicine on the College program April 1.

By resolution, one Associate and two Fellows were dropped from the College Roster because of delinquency of two years' or more standing, action being taken in accordance with provisions of the By-Laws.

Dr. George Morris Piersol reminded the Board that no action had yet been taken on the recommendation of the Committee on Postgraduate Education in regard to an appointment of a committee of the Board of Governors to organize and direct the Postgraduate Courses, this duty being delegated from the Regents' Postgraduate Committee acting in an advisory capacity. Dr. Piersol said that the Regents' Committee would be very glad to have a Committee of Governors to take over the organization, extension and expansion of these Courses, but that they can hardly do it without authority from the Board of Regents. It was suggested that the Regents' Committee be called the Committee on Educational Policy and the Governors' Committee be called the Advisory Committee on Postgraduate Courses.

Dr. Morgan asked for a discussion of the practicability of such a plan by the Executive Secretary, Mr. Loveland.

Mr. Loveland: "I am sure it would be practicable for the Regents' Committee on Postgraduate Education to be a Committee on Policy, the real authoritative committee for contacts with the Conference Committee on Graduate Training in Medicine, the Advisory Council on Medical Education, Licensure and Hospitals, the Council on Medical Education and Hospitals of the American Medical Association, etc., and for this committee, through the Board of Regents, to delegate to a Committee of the Board of Governors the organization and general direction of the Postgraduate Courses. The Board of Governors meets but once a year. Under the Constitution, it has no authority for appropriations. Therefore, the general supervision, including official appropriations and authorization must remain with the Board of Regents. The Board of Governors may very properly have a committee whose sole and primary duty is the conduct of the Postgraduate Courses, but it is recommended that the Chairman of that committee, the working Chairman, be near Philadelphia and the Executive Offices. There are many problems that arise in the course of registering the physicians for these Courses, and it would be a matter of great convenience in their administration to have the Chairman of the committee available for personal conference and advice. Furthermore, there is a crying need to have these Courses organized and announced much earlier in the year. The December meeting of the Board of Regents is too late, especially when one considers that it takes several weeks to get the copy of the detailed courses from each director, to have the bulletins printed and distributed. The Advisory Committee on Postgraduate Courses should have certain authority delegated to it by the Board of Regents, such as to proceed in the preparation of courses immediately after our Annual Session, and to be ready to announce them early in the autumn."

Dr. Bruce: "As I understand it, the Committee on the Board of Governors should assume the responsibility for advising the Regents' Committee; that the final authority, financial and otherwise, shall rest with the Board of Regents, and the Committee of the Board of Governors shall act as an activating or advisory committee, to set up such courses as it be most appropriate."

On motion by Dr. Hugh J. Morgan, seconded by Dr. George Morris Piersol, and regularly carried, it was

Resolved, that the Board of Regents shall have a Committee on Educational Policy, consisting of three members appointed by the President, and that the Board of Governors shall have an Advisory Committee on Postgraduate Courses, appointed after conference between the President and the Chairman of the Board of Governors,

this committee to have the sole duty of organizing the Postgraduate Courses, their decisions to have the approval of the Regents' Committee on Educational Policy.

President Pepper, after reading announcements, addressed the Board as follows:

"It is the sad duty of the President to state that to the best of his knowledge this meeting terminates the service on the Board of Dr. Sydney R. Miller and Dr. Ernest B. Bradley. Both of these gentlemen have been Presidents of the College and have served the College faithfully and long, and only the necessities of the Constitution and By-Laws prevent their continuance. We see their departure from this Board with great regret.

"This meeting terminates my presiding over these meetings, and although I will, of course, be with you, I want to express very briefly my sincere appreciation of your coöperation. Any man of you who has had the slightest chance to coöperate has done so in the fullest extent. I can't imagine a President having things made any easier for him than your efforts have made things for me. The Presidency of this College is a sinecure when they have committees such as those which you all represent.

"I thank you, every one of you."

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

THIRD MEETING, APRIL 5, 1940

The third meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, was held at the Cleveland Public Auditorium, Cleveland, Ohio, April 5, 1940, with Dr. James D. Bruce, President, presiding, fifteen members of the Board present and Mr. E. R. Loveland acting as Secretary.

The Secretary presented an abstract of the transactions of the preceding meeting of the Board in accordance with provisions of the By-Laws.

The meeting proceeded to the election of the Treasurer and the Secretary-General for 1940–41.

On motion by Dr. James E. Paullin, seconded by Dr. Reginald Fitz, Dr. William D. Stroud was nominated for reëlection as Treasurer.

On motion by Dr. D. Sclater Lewis, seconded by Dr. James E. Paullin, and carried, it was

RESOLVED, that nominations for Treasurer be closed and the ballot cast by the Chairman.

Dr. Bruce announced Dr. William D. Stroud duly reëlected Treasurer for 1940–41.

On motion by Dr. James E. Paullin, seconded by Dr. Henry M. Thomas, Jr., Dr. George Morris Piersol was nominated for reëlection as Secretary-General.

On motion by Dr. Charles H. Cocke, seconded by Dr. William J. Kerr, it was

RESOLVED, that nominations for Secretary-General be closed and the ballot cast by the Chairman.

President Bruce announced Dr. George Morris Piersol reëlected Secretary-General for 1940–41.

The Executive Committee for 1940–41 was elected and constituted as follows:

James D. Bruce, Chairman	President
Roger I. Lee	President-Elect
George Morris Piersol	Secretary-General
William D. Stroud	Treasurer
Francis G. Blake	(new election)
Reginald Fitz	(reëlected)
Hugh J. Morgan	(reëlected)
O. H. Perry Pepper	(new election)
Maurice C. Pincoffs	(reëlected)

In accordance with directions and regulations of the Constitution and By-Laws, or of specific resolutions governing committees, the following were appointed by President James D. Bruce:

Committee on Advertisements and Commercial Exhibits

George Morris Piersol, Chairman	(reappointed)
Sydney R. Miller	(new appointment)
William D. Stroud	(reappointed)

Committee on the Annals of Internal Medicine

Walter W. Palmer, Chairman	(1943)	(reappointed)
David P. Barr	(1941)	
Reginald Fitz	(1942)	

Committee on Constitution and By-Laws

Ernest E. Irons, Chairman	(1942)	
J. Morrison Hutcheson	(1941)	
William J. Kerr	(1943)	(new appointment)

Committee on Credentials

George Morris Piersol, Chairman	(1943)	(reappointed)
James G. Carr	(1941)	(new appointment)
Robert A. Cooke	(1942)	(new appointment)
Charles H. Cocke	(1941)	
J. Owsley Manier	(1942)	
William B. Breed	(1943)	(reappointed by Board of Governors)

Committee on Educational Policy

Hugh J. Morgan, Chairman
Charles H. Cocke
Ernest E. Irons

(This Committee is the result of a reorganized plan as provided in the Minutes of the Board of Regents on April 2.)

Advisory Council on Medical Education, Licensure and Hospitals

Hugh J. Morgan	(reappointed)
James H. Means	(reappointed)

Conference Committee on Graduate Training in Medicine

Hugh J. Morgan	(reappointed)
O. H. Perry Pepper	(new appointment)

Advisory Committee on Postgraduate Courses

Edward L. Bortz, Chairman
C. Sidney Burwell
Ernest H. Falconer
Fred M. Smith
James J. Waring

(This Committee, appointed by the Chairman of the Board of Governors in consultation with the Chairman of the Board of Regents, is a new committee as constituted by the Regents on April 2, 1940.)

Committee on Fellowships and Awards

David P. Barr, Chairman	(reappointed)
Francis G. Blake	(reappointed)
Ernest E. Irons	(reappointed)
Jonathan C. Meakins	(reappointed)
Henry M. Thomas, Jr.	(new appointment)

Committee on Finance

Roger I. Lee, Chairman	(1943)	(reappointed)
Charles T. Stone	(1941)	
O. H. Perry Pepper	(1942)	(new appointment)

Committee on Public Relations

James E. Paullin, Chairman	(1943)	
T. Homer Coffen	(1941)	(new appointment)
Gerald B. Webb	(1942)	(new appointment)
Henry M. Thomas, Jr.	(1944)	(new appointment)
James D. Bruce	Ex Officio	

Committee on Revolving Loan Fund

Maurice C. Pincoffs, Chairman	(reappointed)
Egerton L. Crispin	(reappointed)
Roger I. Lee	(reappointed)

Committee on Scientific Exhibits (present committee continued)

Francis G. Blake, Chairman
Robert A. Cooke
D. Sclater Lewis

Committee on Survey and Future Policy

James Alex. Miller, Chairman	(reappointed)
Charles H. Cocke	(reappointed)—Chmn., Bd. of Governors
Roger I. Lee	(new appointment)—Chmn., Finance Com.
Jonathan C. Meakins	(reappointed)—Amer. Bd. of Int. Med.
Hugh J. Morgan	(reappointed)—Com. on Educational Policy
George Morris Piersol	(reappointed)—Chmn., Credentials Com.
Maurice C. Pincoffs	(reappointed)—Editor, A. I. M.

Consulting Committee on Annual Sessions

James D. Bruce, Chairman
William B. Breed
O. H. Perry Pepper
Howard T. Karsner
William J. Kerr
John H. Musser

House Committee

William D. Stroud, Chairman	(reappointed)
T. Grier Miller	(reappointed)
Harry B. Wilmer	(new appointment)

The Regents were reminded that reappointments had already been made to the *American Board of Internal Medicine* at the Regents' meeting, March 31, 1940, which constituted the current board, so far as the American College of Physicians' appointments are concerned, as follows:

William S. Middleton	(1941)
Louis Hamman	(1941)
David P. Barr	(1942)
Jonathan C. Meakins	(1943)
G. Gill Richards	(1943)

President Bruce requested more time to consider appointments to the Committee on Nominations, which he stated would be announced shortly after the Session closed.

President Bruce called for the presentation of communications and invitations for the 1941 Session of the College.

The Secretary, Mr. Loveland, read invitations from Kansas City, the University of Chicago, Philadelphia, Rochester, Baltimore, San Francisco and Boston. These invitations had been initiated by physicians on invitations in the cities named, and for the most part included letters from the deans of medical schools, secretaries and officers of local medical societies, and from such civic agencies as the Chambers of Commerce, Mayors, Governors, etc.

Dr. Roger I. Lee spoke on the invitation from Boston, saying that the Boston profession is very anxious to have the College accept the invitation, and that he felt Boston has all necessary facilities, including especially the clinical facilities. Immediately Dr. Lee moved that the College accept the Boston invitation. The motion was seconded by Dr. James E. Paullin and was opened for discussion.

Dr. Charles H. Cocke, Chairman of the Board of Governors, reported that that Board had also considered the various invitations, and would strongly support that from Boston—in fact, unanimously.

The motion was put to vote and it was unanimously

RESOLVED, that the American College of Physicians shall accept the Boston invitation for its 1941 Annual Session.

Dr. William J. Kerr reminded the Board that San Francisco is ready and strongly desirous of a careful consideration of its invitation for a meeting in San Francisco again in the near future. He said that they would be very happy to have the College think of San Francisco for 1942, and that in the meantime a more formal and complete invitation will be prepared.

President Bruce then asked for suggestions concerning the election of a General Chairman for the 1941 Session and the selection of dates. He suggested that it might be quite appropriate for Dr. Roger I. Lee, Boston Regent, himself and others to confer concerning the appointment of the General Chairman.

On motion by Dr. O. H. Perry Pepper, seconded by Dr. Reginald Fitz, and regularly carried, it was

RESOLVED, that the authority to appoint the General Chairman and select the dates for the 1941 meeting be vested in the President in conference with Dr. Roger I. Lee.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary